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INTEGRATED VECTOR MANAGEMENT PROGRAMS FOR MALARIA VECTOR CONTROL (VERSION 2017)

PROGRAMMATIC ENVIRONMENTAL ASSESSMENT

JANUARY 2017

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Prepared Under: The GEMS II contract (award number AID-OAA-M-13-00018)

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ACRONYMS

ACHE	acetylcholinesterase
ADD	average daily dose
ATSDR	Agency for Toxic Substances and Disease Registry
BEO	Bureau Environmental Officer
BMP	best management practice
Bs	*Bacillus sphaericus*
Bti	*Bacillus thuringiensis israelensis*
CAS	Chemical Abstracts Service
CDC	Centers for Disease Control and Prevention
CFR	U.S. Code of Federal Regulations
CHE	cholinesterase
CS	capsule suspension
CSF	cancer slope factor
DAF	dilution and attenuation factor
DDT	dichlorodiphenyltrichloroethane
EA	environmental assessment
EC	emulsifiable concentrate
EC50	median effective concentration
EIR	entomological inoculation rate
EOL	end of life
ESLs	ecological screening levels
EXTOXNET	EXtension TOXicology NETwork
GFATM	Global Fund for AIDS, Malaria and Tuberculosis
GRAM	generic risk assessment model
GUP	general use pesticide
HAARP	harmonized approach for the assessment of risk in programmatic environmental assessments
HI	hazard index
HQ	hazard quotient
HSDB	Hazardous Substances Data Bank
HSS	U.S. Department of Health and Human Services
IEE	initial environmental examination

ILCR	incremental lifetime cancer risk
IRS	indoor residual spraying
ITN	insecticide-treated net
IVM	integrated vector management
LADD	lifetime average daily dose
LC50	median lethal concentration
LD50	lethal dose, 50 percent of the test population
LLIH	long-lasting insecticidal hammock
LLIN	long-lasting insecticidal net
LOAEL	lowest observed adverse effect level
LSM	Larval source management
MEO	Mission Environmental Officer
MF	modifying factor
MOE	margin of exposure
MOH	Ministry of Health
MOS	Margin of Safety
MRL	minimal risk level
MRLs	maximum residue limits
MSDS	material safety data sheet
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NMCP	National Malaria Control Program
OP	organophosphate
PBO	piperonyl butoxide
PEA	programmatic environmental assessment
PERSUAP	pesticide evaluation report and safer use action plan
PMI	President's Malaria Initiative
POPs	persistent organic pollutants
PPE	personal protective equipment
PQ	WHO Prequalification Team
PSCs	pyrethrum spray catches
RED	re-registration eligibility decision
REO	Regional Environmental Officer
RfD	reference dose

RNA	ribonucleic acid
RUP	restricted use pesticide
SEA	supplemental environmental assessment
SF	safety factor
SOP	standard operating procedure
UF	uncertainty factor
ULV	ultra-low volume
UNFAO	Food and Agriculture Organization of the United Nations
UNICEF	United Nations International Children's Emergency Fund
USAID	U.S. Agency for International Development
USEPA	United States Environmental Protection Agency
WHO	World Health Organization
WHOPES	WHO Pesticide Evaluation Scheme
WP	wettable powder

APPROVAL OF THE RECOMMENDED ENVIRONMENTAL ACTION FOR THE PROGRAMMATIC ENVIRONMENTAL ASSESSMENT FOR THE INTEGRATED VECTOR MANAGEMENT PROGRAM FOR MALARIA VECTOR CONTROL (2016 UPDATE)

CLEARANCE:

Office Director, GH/ID	Signed via-email Elizabeth Fox	Date: 1/18/2017
Global Health Bureau Environmental Officer	Signed  Rachel Dagovitz	Date _____

ADDITIONAL CLEARANCES

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Asia Bureau Environmental Officer	Signed via-email Will Gibson	Date: 1/31/2017
DCHA Bureau Environmental Officer	Signed via-email Erica Clesceri	Date: 1/30/2017
Division Chief, GH/ID/Malaria	Signed via-email Julie Wallace	Date: 1/23/2017

EXECUTIVE SUMMARY

Global progress on malaria control has been unequivocal – the World Health Organization (WHO) estimates that more than 6.2 million malaria deaths were averted worldwide between 2000 and 2015. Most of the estimated lives saved were children under the age of five living in sub-Saharan Africa. Progress is the collective result of significant and well-coordinated investments by national governments and donors, support from technical agencies and national institutions, and the hard work and dedication of health workers, non-governmental organizations, and affected communities.

The U.S. Government's leadership and its financial and technical contributions – primarily through the President's Malaria Initiative (PMI) – have been central to this progress. PMI, launched in 2005 by President George W. Bush and expanded by President Barack Obama, supports the rapid scale-up of proven and highly effective malaria prevention and treatment measures. PMI is an interagency initiative led by the United States Agency for International Development (USAID) and implemented together with the U.S. Centers for Disease Control and Prevention of the U.S. Department of Health and Human Services.

The WHO recommends that endemic countries protect all those at risk of malaria with long-lasting insecticide treated nets (LLINs) and/or, where appropriate, indoor residual spraying (IRS). The scale-up of these two proven and highly effective vector control measures is among PMI's greatest accomplishments. To date, PMI has procured more than 197 million LLINs, and in FY 15, protected more than 16 million people with IRS. In PMI-supported countries, household ownership of at least one insecticide-treated net (ITN) increased from a median of 29% (baseline survey) to 60% (most recent survey), and usage of an ITN the night before the survey increased from a median of 18% to 46% and more than doubled from 17% to 41% for children less than five years of age and pregnant women, respectively. USAID also supports malaria control activities in the Amazon (Amazon Malaria Initiative) and in emergency situations (through its Bureau for Democracy, Conflict, and Humanitarian Assistance).

Globally, the proportion of the population sleeping under an ITN has increased dramatically in sub-Saharan Africa since 2000. Almost three-quarters (67%) of the population in sub-Saharan Africa had access to an LLIN in 2015, compared to less than 2% in 2000, and the estimated proportion sleeping under an LLIN was 55% (WHO's *World Malaria Report 2015*). Given that spraying is a more targeted intervention (as opposed to universal coverage for nets), approximately 6% of the population at risk of malaria in Africa live in households that are protected by IRS.

Despite these gains, malaria remains the most important vector-borne disease in public health. According to the latest estimates from WHO, there were 214 million new cases of malaria and 438,000 malaria deaths worldwide in 2015. Children under five are particularly susceptible to malaria illness, infection, and death. In 2015, malaria killed an estimated 306,000 children under five years of age globally, including 292,000 children in the African Region. Malaria also exacts a significant economic toll – large fractions of health sector budgets are spent on malaria control and treatment, and disproportionate fractions of household income are spent on preventing and treating malaria. Among those at highest biological risk of malaria are children under five years of age and pregnant women, and malaria infections during pregnancy create substantial risks for pregnant women and their fetuses and newborns. As such, malaria prevention and control remain a major U.S. foreign assistance objective. Under the PMI Strategy 2015-2020, the U.S. Government's goal is to work with PMI-supported countries and partners to further reduce malaria deaths and substantially decrease malaria morbidity, toward the long-term goal of elimination. In order to achieve this goal, the U.S. Government will continue to focus, in part, on scaling-up and/or maintaining high levels of protection with proven and highly effective, life-saving vector control measures.

As a federal government agency, USAID is subject to Title 22, Code of Federal Regulations, Part 216 (22 CFR), known as Regulation 216, to define USAID's environmental impact assessment procedures. Because LLINs and IRS rely on insecticides to kill or reduce the lifespan of female mosquitoes, and because the geographic coverage of these interventions is expansive and multi-country/multi-continent, a Programmatic Environmental Assessment (PEA) approach is warranted for meeting Regulation 216 requirements and

providing the protocols that assure the environmental soundness of project implementation. A PEA serves as an umbrella evaluation of environmental and human health issues, thereby streamlining the preparation of country- and activity-specific environmental assessments and promoting implementation of activities that adhere to uniform standards and best practices.

Over the last 14 years, two PEAs have been prepared to evaluate potential environmental and human health effects from the implementation of malaria vector control interventions. In 2002, USAID identified the need for insecticide-treated materials as an important tool in the integrated malaria control program, and prepared the *Programmatic Environmental Assessment for Insecticide-Treated Materials in USAID Activities in Sub-Saharan Africa*, which addressed the risks associated with the use of insecticide-treated materials. In 2007, the second PEA (*The Integrated Vector Management Programs for Malaria Vector Control Programmatic Environmental Assessment)* was prepared to address the expansion of USAID's malaria vector control programs; specifically, to address the human and environmental risks associated with IRS, ITNs, and larviciding. Integrated vector management is a rational decision-making process for the optimal use of resources for vector control and one of the guiding principles behind the PEA. In 2012, the *Integrated Vector Management Program for Malaria Vector Control PEA* was revised to assess new active ingredients/formulations for IRS, ITNs, and larviciding.

This second and current revision to the 2007 PEA is substantial in both the number of new products and interventions that were assessed. The imminent arrival of new active ingredients, or new combinations of active ingredients, is essential in combatting insecticide resistance. Insecticide resistance is one of the most serious threats to malaria control, and resistance management is a key component of integrated vector management. Historically, IRS has relied on a limited number of WHO-recommended insecticides from only four insecticide classes, and ITNs have relied solely on pyrethroids. This revision characterizes the potential human health and environmental risks associated with the following active ingredients or combinations of active ingredients for IRS and LLINs[1]:

ACTIVE INGREDIENTS FOR IRS ASSESSED IN THIS REVISION

- Chlorfenapyr suspension concentrate (Phantom)
- Clothianidin water dispersible granules (Sumishield)
- Clothianidin and deltamethrin wettable powder in sealed water soluble bag (Fludora Fusion)
- Pirimiphos-methyl capsule suspension (Actellic CS)

ACTIVE INGREDIENTS FOR LLINS ASSESSED IN THIS REVISION

- Alpha-cypermethrin and pyriproxyfen on polyethylene (Royal Guard)
- Alpha-cypermethrin on polyethylene (Royal Sentry)
- Alpha-cypermethrin and chlorfenapyr on polyester (Interceptor G2)
- Permethrin and pyriproxyfen on polyethylene (Olyset Duo)
- Permethrin and piperonyl butoxide on polyethylene (Olyset Plus)
- Deltamethrin on polyethylene (Panda Net 2.0)

The current revision of the PEA also expands the suite of active ingredients assessed for larviciding, and includes, for the first time, mitigation measures for larviciding. While it is envisaged that USAID will continue to rely on LLINs and IRS as the primary vector control interventions, USAID may utilize larviciding agents, particularly in pre-elimination and elimination settings, depending on the vector and country-specific

[1] It is important to note that the results are not product-specific, even if product names are listed; for example, if an LLIN with a concentration of *X* mg/m^2 for permethrin and *Y* mg/m^2 for pyriproxyfen on material *A* is assessed, any LLIN with concentrations at or below *X* and Y mg/m^2 for permethrin and pyriproxyfen, respectively, on material *A* would not have to undergo another risk assessment in the PEA.

environmental conditions. New is the characterization of the potential human health and environmental risks associated with the following active ingredients or combinations of active ingredients for larvicidal agents:

ACTIVE INGREDIENTS FOR LARVICIDAL AGENTS

- Pyriproxyfen
- Spinosad
- Spinosad 83.3 monolayer
- Spinosad 25 extended release
- Chlorpyrifos
- Diflubenzuron
- Novaluron
- Fenthion
- Methoprene
- Pirimiphos-methyl
- Temephos
- *Bacillus thuringiensis israelensis* (strain AM65-52, 3000 ITU/mg)
- *Bacillus thuringiensis israelensis* (strain AM65-52, 200 ITU/mg))
- *Bacillus thuringiensis israelensis* (strain AM65-52 + *Bacillus sphaericus* strain ABTS-1730; 50 Bsph ITU/mg)
- *Bacillus thuringiensis israelensis* (strain 266/2, $\geq$ 1200 ITU/mg)

This revision also assesses the safety of clothing treated with permethrin and long-lasting insecticidal hammocks treated with permethrin and with deltamethrin to enable USAID to support the deployment of such interventions when/where appropriate.

The four other primary purposes for this PEA update are summarized below:

(1) Harmonizing the methodology used to calculate potential risks in the PEA with WHO's Generic Risk Assessment Models for insecticides, which were all released after the first PEA was drafted.
(2) Streamlining the PEA methodology, emphasizing a more modular approach to allow USAID to more quickly assess the potential risks for new interventions and insecticides.
(3) Refining mitigation measures based on a decade of experience with malaria vector control activities, and focusing mitigation measures on the pathways of greatest concern for risks from insecticide exposures.
(4) Standardizing the risk assessment results to allow comparisons between insecticides within and among interventions, and between different pathways of exposure. This standardization will enable a PEA user/decision-maker to determine what exposure scenarios and pathways tend to be riskiest, identify which individuals are likely to receive the highest exposures, and compare the relative risks of insecticides approved for a specific intervention.

The revised methodology in this PEA draws on the exposure and risk assessment methods described in the previous two USAID vector control PEAs and revisions, the WHO's Generic Risk Assessment Models for IRS, ITNs, and larviciding, and guidance documents and standard operating procedures published by the U.S. Environmental Protection Agency and the U.N. Food and Agricultural Organization. It is important to note that there is uncertainty with respect to the form of the exposure equations (i.e., does the equation adequately represent actual exposure conditions and processes), and uncertainty and variability associated with the input parameter data used in the calculations. Conservative (i.e., overstating risk) input values were used to ensure potential risk was not underestimated.

One aspect of the health risk characterization is based on the hazard quotient (HQ) for noncancer effects. The threshold criterion for noncancer effects is an HQ of 1; HQ values below 1 strongly indicate that significant adverse effects are not expected, and HQ values above 1 indicate that adverse noncancer effects are possible. The quantitative screening of noncancer hazard is a binary outcome, and does not provide

information on the probability that an adverse effect will occur. However, given the conservative assumptions employed in the exposure assessments, the HQ represents a value at the upper bound of the inferred distribution of chemical hazard for exposed individuals. For that reason, the interpretation of the noncancer screening results is critical in determining how the risk assessment results are used. Put simply, an HQ of 10 does not imply that adverse effects *will* occur, or that the hazard is ten times more likely than with an HQ of 1. Rather, an HQ of 10 implies that it is possible that they occur given the conservative manner in which the exposure scenario was constructed, and that further evaluation of the exposure assumptions is warranted.

The other health risk characterization is based on the incremental lifetime cancer risk (ILCR) for carcinogenicity. For cancer risk, a threshold ILCR of 1 in 10,000 (1E-04) is used as the acceptable excess risk of an individual contracting cancer over a lifetime. ILCR values below 1E-04 indicate that the risk of cancer is relatively low even though it is non-zero. Unlike an HQ, the ILCR is expressed as a probability. This probability is based on the dose-response model of carcinogenicity and does not address the probability of an individual actually being exposed to an insecticide at a level that causes cancer. Therefore, an ILCR above 1E-04 should not be interpreted to mean that an individual is actually likely to experience this cancer risk; rather, this should be interpreted in much the same way we interpret a screening HQ greater than 1. Cancer risks greater than 1 in 10,000 suggest that it is possible risk of cancer may exceed the threshold, but consideration should be given to the conservative manner in which the exposure scenario was constructed.

The revised PEA contains full risk results, both in tabular and graphic form, of products assessed for the first time in this PEA revision, and updated/standardized risk results for all products previously assessed, to allow for comparisons. Because cancer risks are only calculated for two LLIN products, below is a summary of the noncancer risks only.

IRS RISK SCREENING RESULTS

Based on the risk screening results, adverse human health effects for workers and residents (all age categories) are not expected from the use of Phantom, Sumishield, or Fludora Fusion in IRS (all HQs were less than 1). In addition, adverse human health effects for workers are not expected from the use of Actellic CS (the HQ was slightly above 1 for workers in the "wearing no PPE" category only). The potential for noncancer effects indicated by the risk screening for Actellic CS in IRS suggests that additional precautions should be explored by USAID, as HQs for adults, children, toddlers, and infants were 6.7, 12, 49, and 25, respectively. The dermal pathway is the driving factor behind the HQ for toddlers. In the next year, PMI will support an operational research study with Actellic CS to determine if spraying only the top half of a wall surface is as effective as spraying the whole surface of the wall; results of the operational research study will be used, in part, to refine standing operating procedures and, if spraying the top half only is deemed effective, then this practice will negate toddlers' dermal exposure pathway. The inhalation pathway is the driving factor behind the HQ for infants, given their high respiratory rate (relative to body weight) compared with other age groups. The risk associated with this pathway is based on the volatilization of IRS after spraying, which is uncertain and conservatively estimated. Additional data on residual insecticide volatilization rates would improve risk estimates and likely lower the calculated noncancer hazard from IRS, especially for infants.

LLIN RISK SCREENING RESULTS

Four of the six LLIN products (Interceptor G2, Royal Guard, Royal Sentry, and Panda Net 2.0) assessed in this PEA revision have similar risk profiles because they contain synthetic pyrethroids (i.e., either deltamethrin or alphacypermethrin) with similar properties. Adverse human health effects for adults and children are not expected from the use of these four products for LLINs (all HQs were less than 1). Risk results are suggestive of *some* potential for adverse health effects for infants and toddlers. Hazard quotients for toddlers were greater than 1 but less than 10 for all four products. Hazard quotients for infants were 9.8, 15, 17, and 6.8 for Interceptor G2, Royal Guard, Royal Sentry, and Panda Net 2.0. However, the oral pathway is the driving factor behind the HQs for toddlers and infants. The highly conservative assumption underlying this pathway, established by the WHO and based on conventionally treated ITNs (not LLINs), is that infants

and toddlers mouth, chew, or suck on a different 50-cm^2 area of net each night, ingesting 33% of the insecticide in that area in the process. Relaxing this assumption even moderately (e.g. dropping the percent of dislodgeable pesticide from 33% to 10%) would reduce all HQs to less than 10.

The HQs of the two permethrin-based LLIN products (Olyset Plus and Olyset Duo) were similar; adverse human health effects for adults and children for both products are not expected (all HQs were less than 1). The HQ for infant for Olyset Duo and the HQs for toddler and infant were in small exceedance of 1, presenting minimal risk to human health. ILCR results for Olyset Plus and Olyset Duo were 5E-04, which is above the threshold of 1E-04. Potential exposures have been summed for the four age cohorts, protectively implying continuous exposure to a permethrin-containing net during a 50-year residential exposure duration. This and other conservative assumptions and models applied to estimate ILCR for LLINs suggest that even a reasonably protective estimate of ILCR is likely to be less than 1E-04.

LARVICIDING RISK SCREENING RESULTS

All larvicides considered in this PEA presented very low health risk to both workers applying the products and residents coming into contact with them via drinking or bathing in contaminated ground water. For chemical larvicides, HQs are well below 1 for all receptors, indicating minimal noncancer hazard, and the ILCR calculated for the one product deemed potentially carcinogenic (diflubenzuron) was well below the threshold of 1E-04, indicating minimal excess cancer risk. Biological larvicides derived from bacteria (primarily *Bacillus thuringiensis*, or Bt) were evaluated qualitatively and determined to present no known human health risks as well.

Ecological risks for larvicide use were considered semi-quantitatively, and show wide variability among products in terms of potential hazard to aquatic and terrestrial ecosystems. While data are somewhat sparse, in general, there is evidence of low risk for at least some larvicide products in most risk categories considered (i.e., persistence, bioaccumulation, and toxicity in various terrestrial and aquatic ecological communities). Results from this PEA can support the selection of preferred larviciding agents under various scenarios of environmental concern.

LONG-LASTING INSECTICIDAL HAMMOCKS (ILIH) AND CLOTHING RISK SCREENING RESULTS

Noncancer effects associated with LLIH are relatively low, with HQ below 1 in most cases. Infant and toddler risks are somewhat higher for both insecticides considered (i.e., permethrin and deltamethrin), but HQs remain below 10 in all cases. Calculated ILCR for permethrin-treated LLIH is 2E-03, considerably higher than the 1E-04 threshold for cancer risks. However, LLIH risk calculations are based on the same conservative assumptions noted above for LLIN. Additional conservatism applies in terms of the permethrin ILCR, in that the risk model used assumes maximal exposure to LLIH during every day of the receptor's lifetime; in reality, LLIH use is unlikely to be continuous, and insecticide concentrations will decline over the course of the product's useful life. Thus, on the basis of all factors considered LLIH are recommended as safe interventions.

Permethrin-treated clothing was evaluated qualitatively in terms of potential for human health risk. In light of its extensive use history (in particular, by the U.S. military) and past evaluations by the USEPA, the intervention is deemed effective and safe for use.

MITIGATION MEASURES

USAID, most often under PMI, works in partnership with Ministries of Health to determine the optimal use of resources for malaria vector control based on factors such as insecticide resistance patterns (including resistance intensity), social acceptability, donor/resource landscape, logistical feasibility, etc. Once an intervention has been selected as appropriate, the choice (if one exists) of insecticide for that intervention is based on the status of WHO recommendation, country registration, duration of malaria season versus

residual efficacy of insecticide, insecticide resistance, cost, safety, and availability of product. All things being equal, USAID strives to select intervention options that pose the least risk to human health and the environment. However, there are currently wide variations in most of these factors (e.g., residual efficacy ranges from two months to eleven months, cost ranges from $3.50 to $23.50 USD a sachet, etc.). As such, the PEA recognizes the trade-offs that are considered when selecting the intervention/insecticide, and has refined its mitigation measures to minimize the likelihood of adverse human health and ecological impacts.

This PEA revision contains results of the pirimiphos-methyl (capsule suspension) biomonitoring pilot that was called for in the 2012 PEA revision, and the ensuing policy recommendation regarding use of pirimiphos-methyl. This PEA revision also contains the revised best practices related to misuse of LLINs (particularly misuse of nets for fishing); updates on global policy discussions regarding end-of-life options for LLINs; and the inclusion of mitigation measures for larviciding programs for malaria control. Intervention-specific mitigation measures are now contained in annexes to allow for rapid revisions to mitigation measures as needs arise.

GOING FORWARD

Historically, *USAID's Integrated Vector Management Programs for Malaria Control PEA* has been revised every four to five years. The modularization of this PEA was designed, in part, to allow for more frequent updates to keep pace with new products. As products are submitted to the WHO for review, manufacturers are highly encouraged to submit the relevant information to USAID for simultaneous review. Revisions to the PEA will thus be made on a more frequent basis.

1.0 INTRODUCTION

The global health vision of the Unites States Agency for International Development (USAID) is a world where people lead healthy, productive lives and where mothers and children thrive. USAID's efforts to combat malaria contribute significantly to two of the priority areas that contribute to achieving this vision: ending preventable child and maternal deaths and fighting infectious diseases. The majority of USAID-supported malaria activities are implemented under the President's Malaria Initiative (PMI) (see below), although USAID also supports malaria control activities in the Amazon (Amazon Malaria Initiative) and in emergency situations (primarily via the Bureau for Democracy, Conflict, and Humanitarian Assistance).

1.1 PRESIDENT'S MALARIA INITIATIVE (PMI)

PMI is an interagency initiative led by USAID and implemented together with the U.S. Centers for Disease Control and Prevention (CDC) of the U.S. Department of Health and Human Services (HHS). It is overseen by a U.S. Global Malaria Coordinator and an Interagency Advisory Group made up of representatives of USAID, CDC/HHS, the Department of State, the Department of Defense, the National Security Council, and the Office of Management and Budget.

When it was launched in 2005, the goal of PMI was to reduce malaria-related mortality by 50% across 15 high-burden countries in sub-Saharan Africa through a rapid scale-up of four proven and highly effective malaria prevention and treatment measures:

1. indoor residual spraying (IRS),
2. long-lasting insecticidal nets (LLINs),
3. intermittent preventive treatment of pregnant women, where appropriate, and
4. treatment with artemisinin-based combination therapies, ideally based on a laboratory diagnosis of malaria.

With the passage of the Tom Lantos and Henry J. Hyde Global Leadership against HIV/AIDS, Tuberculosis, and Malaria Act in 2008, PMI developed a U.S. Government Malaria Strategy for 2009–2014. This strategy included a long-term vision for malaria control in which sustained high coverage of malaria prevention and treatment interventions would progressively lead to malaria-free zones in Africa, with the ultimate goal of worldwide malaria eradication by 2040–2050. Consistent with this strategy and the increase in annual appropriations supporting PMI, four new sub-Saharan African countries and one regional program in the Greater Mekong Subregion of Southeast Asia were added in 2011. The contributions of PMI, together with those of other partners, have led to dramatic improvements in the coverage of malaria control interventions in 19 PMI-supported countries, 17 of which have documented substantial declines in all-cause mortality rates among children less than five years of age.

The current PMI Strategy (2015–2020) takes into account the progress over the past decade and the new challenges that have arisen, setting forth a vision, goal, objectives, and strategic approach for PMI through 2020, while reaffirming the longer-term goal of worldwide malaria eradication. Malaria prevention and control remain a major U.S. foreign assistance objective, and this strategy fully aligns with the U.S. Government's vision of ending preventable child and maternal deaths and ending extreme poverty. It is also in line with the goals articulated in the Roll Back Malaria partnership's second *Global Malaria Action Pla*n and the World Health Organization's (WHO) *Global Technical Strategy*. The U.S. Government shares the long-term vision of affected countries and global partners of a world without malaria. This vision will require sustained, long-term efforts to drive down malaria transmission and reduce malaria deaths and illnesses, leading to country-by-country elimination and eventual eradication by 2040–2050. The U.S. Government's goal is to work with PMI-supported countries and partners to further reduce malaria deaths, substantially decrease malaria morbidity, and move toward the long-term goal of elimination.

Progress to Date – Since 2000, there has been tremendous scale up of malaria prevention and control measures, particularly in sub-Saharan Africa. In 2015, almost three-quarters (67%) of the population in sub-

Saharan Africa had access to an LLIN, compared to less than 2% in 2000. The estimated proportion sleeping under an LLIN was 55%. Under the PMI alone, 197 million LLINs have been procured since the launch of the initiative. In addition, 116 million people globally were protected by IRS in 2014, including 50 million people in Africa. Approximately 6% of the population at risk of malaria in Africa live in households that are protected by IRS.

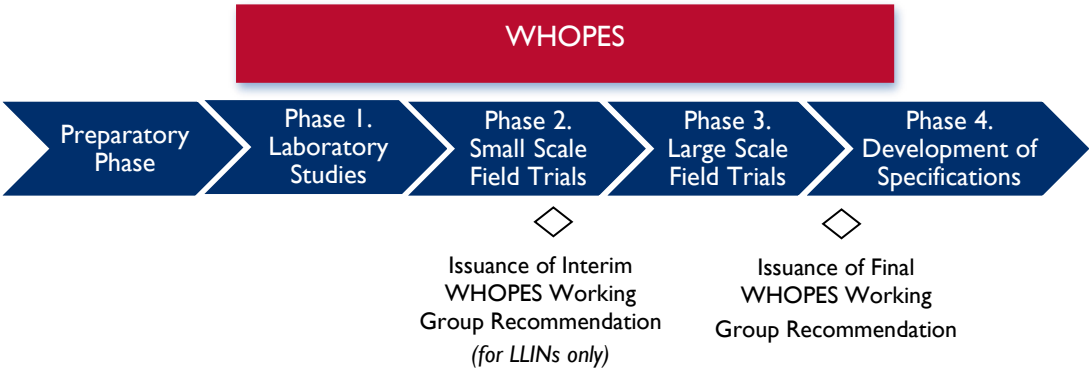
This scale up has led to unequivocal global progress in malaria control. Between 2000 and 2015, malaria mortality rates fell by 60% globally and by 66% in the African region, and the WHO estimates that more than 6.2 million malaria deaths were averted during this period. Malaria is no longer the leading cause of death among children under five in sub-Saharan Africa. In the 17 PMI focus countries that have paired nationwide surveys conducted since 2006, there have been significant declines in all-cause mortality rates among children less than five years of age, ranging from 8% to 67%.

Global Burden of Disease – According to the latest estimates from WHO, there were 214 million new cases of malaria worldwide in 2015 (range 149–303 million). The African Region accounted for most global cases of malaria (88%), followed by the South-East Asia Region (10%) and the Eastern Mediterranean Region (2%).

In 2015, there were an estimated 438,000 malaria deaths (range 236,000–635,000) worldwide. Most of these deaths occurred in the African Region (90%), followed by the South-East Asia Region (7%) and the Eastern Mediterranean Region (2%). Children under five are particularly susceptible to malaria illness, infection and death. In 2015, malaria killed an estimated 306,000 children under five years of age globally, including 292,000 children in the African Region.

Regulatory Setting – As a federal government agency, USAID is subject to U.S. environmental laws and regulations. Implementation of these through environmental impact assessments ensures that USAID development programs are both economically and environmentally sustainable. Title 22, Code of Federal Regulations, Part 216 (22 CFR 216), more often called Regulation 216, defines USAID's environmental impact assessment procedures. Regulation 216, Section 216.6 (d) states that "Program Assessments may be appropriate in order to: assess the environmental effects of a number of individual actions and their cumulative environmental impact in a given country or geographic area; or the environmental impacts that are generic or common to a class of agency actions; or other activities which are not country-specific." Based on the nature of the proposed activities and geographic coverage, a Programmatic Environmental Assessment (PEA) approach is warranted for meeting Regulation 216 requirements and provides the protocols that assure the environmental soundness of project implementation. A PEA also expedites future USAID environmental documentation processes by providing reference material for Initial Environmental Examinations (IEEs), Supplemental Environmental Assessments (SEAs), or other individual environmental assessments that address country-specific USAID support for malaria vector control activities.

The WHO's Pesticides Evaluation Scheme (WHOPES) is the program charged with promoting and coordinating the testing and evaluation of pesticides for public health. It oversees the phased evaluation of pesticide products and produces international recommendations. It functions through the participation of



representatives of governments, manufacturers of pesticides and pesticide application equipment, WHO Collaborating Centres and research institutions, as well as other WHO programs, notably the International Programme on Chemical Safety. Currently, WHOPES employs a phased evaluation and testing program as follows:

Upon submission of a dossier from the manufacturer (which includes a manufacturer-generated risk assessment), WHOPES begins its review, assessing whether additional data is required and defining trial protocols. During Phase 1, the properties of the product (i.e., biological efficacy and residual effect) are evaluated in a laboratory setting and an independent risk assessment is completed. During Phase 2, the product properties (i.e., biological efficacy and impact on vector behavior) are evaluated, and perceived adverse effects on users are investigated, in small-scale field trials. During Phase 3, the product is evaluated for its residual activity and operational acceptability in large-scale field trials. Upon satisfactory completion of WHOPES Phases 1 through 3, WHO specifications of the product are developed and published in collaboration with the Food and Agriculture Organization of the United Nations (UNFAO). These specifications – which describe physical and chemical characteristics – provide countries a point of reference for quality control. For LLINs, WHOPES issues an *interim* recommendation of the product after successful completion of Phase 2 and the product then becomes eligible for procurement by donors.[2]

While WHOPES is not a regulatory body, its rigorous independent review is critical, and Member States that lack the capacity to conduct their own risk assessments often rely on WHOPES for the development of policies, strategies, and guidelines for the selective and judicious application of public health pesticides. In addition, WHOPES recommendations are often a necessary precursor to country registration. As such, while USAID is not required by US regulations to select insecticide products that have been recommended for use by WHOPES, most countries where USAID supports vector control interventions will only register insecticide products recommended by WHOPES. Therefore, USAID's procurement policies factor in WHOPES recommendations in its environmental decision making criteria (see Annex B and Section 2 for more information).

Over a 3-year transition process starting October 2015, pesticide evaluation will move to the WHO Prequalification Team (PQ), which has been performing a similar function (assessing the quality, safety, and efficacy) for pharmaceuticals since 2001. WHOPES will continue to coordinate and supervise the testing of pesticide products for any trials that are in process or for products accepted into WHOPES before October 2016. WHOPES will organize the last Working Group meeting during the first quarter of 2017. Thereafter, any data generated from pesticide trials will be assessed by the PQ under the new vector control product assessment team. USAID is in support of these changes, and has been collaborating with WHO through the Gates-funded "Innovation to Impact" project to facilitate a timely and smooth transition to the new review process. When the specifics of the new process have been determined, relevant sections of the PEA and/or annexes will be revised to reflect the new process.

1.2 PURPOSE OF THIS PEA UPDATE

The PEA serves as an umbrella evaluation of environmental and human health issues related to malaria vector control and assists with the preparation of country and activity specific SEAs for malaria vector control programs. Importantly, the PEA provides project managers with a technical, policy, and procedural guide for the preparation of country- and activity-specific SEAs for individual malaria vector control programs. Together, the PEA and SEAs are intended to provide a clear basis for how malaria vector control activities should be implemented to comply with the Agency's environmental regulations. This PEA fulfills the legal requirement of assessing environmental and health impacts of the Malaria Vector Control Program

2 There is only one instance to date where an LLIN product with a WHOPES interim recommendation following the completion of its Phase 2 testing did not pass the Phase 3 testing, at which point the interim recommendation was withdrawn (and donors immediately stopped procuring the product).

and it is a tool for designing and implementing safe, environmentally, and socially sound malaria vector control activities.

This is the second revision to the PEA (the original was released in 2007 and the first revision was released in 2012). There are five primary purposes for this PEA update:

1. harmonize the methodology with the Generic Risk Assessment Models (GRAMs) for insecticides published by the WHO;
2. streamline the PEA methodology, emphasizing a more modular approach;
3. characterize potential health and environmental risks associated with new interventions and active ingredients;
4. refine the mitigation measures based on a decade of experience with malaria vector control activities; and
5. standardize the risk assessment results to allow comparisons between insecticides within an intervention, interventions, pathways of exposure, and individuals that come in contact with insecticides in work and residential settings.

Harmonized PEA Methodology – Since the PEA risk assessment methodology was developed in 2007, the WHO has published three GRAMs: Indoor Residual Spraying – First Revision (WHO, 2011), Insecticide Treated Nets – Revised Edition (WHO, 2012), and Larvicides – First Revision (WHO, 2011). The GRAM is similar in many respects to the methodology in the 2007 PEA (both drew heavily from U.S. Environmental Protection Agency (USEPA) references and data sources); however, there are differences regarding exposure scenarios (e.g., how exposure occurs), and the risk calculations are presented differently in the respective reports. As a result, industry submissions on insecticide risk assessment are not easily interpretable relative to the 2007 PEA methodology, and the comparison between risk assessments is unnecessarily time consuming. Therefore, the **H**armonized **A**pproach for the **A**ssessment of **R**isks in **P**rogrammatic Environmental Assessments (HAARP) was developed for this PEA revision. The HAARP is organized around intervention (rather than activities like mixing insecticides), and explicitly tracks exposure scenarios with the risk calculations and necessary input data. This allows USAID to easily replicate the calculations and demonstrate that best risk assessment practices have been followed. In addition, the evaluation of the Affected Environment is now focused primarily on larviciding; while environmental implications of end-of-life issues (e.g., disposal recommendations) are included under the discussion of each intervention type.

Streamlined Methodology –Because previous PEAs were not modular previously, updating the PEA required a relatively long period of time. The ability of USAID to rapidly assess (and utilize) new interventions and/or new products is critical.

- The document has been reorganized such that only a few sections will need to be updated each time USAID approves a new intervention or product (e.g., Section 4.0, Annex C).
- The level of technical detail has been reduced in the main body of the report and, generally, the HAARP avoids duplicating readily available risk assessment guidance documents.
- The report is now organized around interventions (rather than exposure pathways) to facilitate information updates and to make new information easy to locate, although the risk calculations for each intervention still involve exposure pathways.
- The exposure scenarios are presented in detail in Annex G, and mapped to the risk calculation equations for each intervention.
- The results section in the main body of the report (Section 4.0) provides a concise summary of the results, inputs, and conclusions.
- Risk calculation software has been developed to provide an efficient method to update input data, add interventions and/or products, run calculations, and analyze results.
- Recommended mitigation measures for IRS, LLINs, and larvicidal agents have been moved to Annexes to allow for rapid review and approval of updated measures.

Apart from revising the PEA to assess new interventions and/or new products, it is expected that USAID will revise the PEA on an ad hoc basis as the need arises (e.g., to refine mitigation measures, to address unforeseen challenges, etc.). At minimum, the PEA will be revised every five years if there are no triggers up to that point requiring a revision. Updates may be proposed by environmental officers, PMI team members, or other technical USAID stakeholders. Substantive changes may require review and clearance by the original signatories.

New Interventions and Product Formulations – This PEA update includes two interventions that have not previously been evaluated by USAID (insecticide-treated clothing and long-lasting insecticidal hammocks (LLIHs)), as well as new product formulations that combine insecticides and/or include an insecticide synergist. In addition, given larviciding may be implemented (when/where determined effective) in pre-elimination and elimination settings, USAID decided to evaluate the full suite of compounds and formulations for the control of mosquito larvae recommended by WHOPES, including biological and chemical agents.

Refined Mitigation Measures – USAID has gained a decade of experience in implementing LLIN and IRS programs, largely under the PMI and to some extent from humanitarian interventions funded by the Office of Foreign Disaster Assistance implemented through non-governmental organizations and public international organizations. Therefore, the mitigation measures for LLINs and IRS in this revised PEA reflect that experience and focus on mitigation measures for the pathways of greatest potential for risk. In addition, this revised PEA includes results from a pilot organophosphate (OP) biomonitoring project and PMI's summarizes ensuing policy recommendation, as well as refined mitigation measures to address LLIN misuse, repurposing, and disposal.

Standardized Results – As the "library" of risk assessment results continues to grow, USAID is developing a greater understanding of the nature and potential magnitude of risks to human health. This knowledge base supports detailed analyses of the risk results, allowing a PEA user/decision-maker to determine what exposure scenarios tend to be riskiest, identify which receptors are likely to receive the highest exposures, and compare insecticides approved for a specific intervention. The insights that USAID develops through these results-mining activities will facilitate the decision-making process and inform continuing development of mitigation strategies.

This PEA was prepared using best practice methodologies as recommended by Regulation 216. This included using numerous secondary sources found in professional journals and in publications by environmental and public health organizations, such as WHO, WHOPES, USAID, USEPA, and others. USAID Malaria Advisors and USAID Environmental Officers were consulted for updated information. Public consultation and review was invited during the scoping process and review of the initial draft of the PEA.

1.3 UNDERSTANDING VECTOR CONTROL

Malaria remains the most important vector-borne disease in public health and the current intensification of malaria control efforts includes the delivery of a package of vector control interventions aimed at controlling transmission.

Malaria is caused by *Plasmodium* parasites. The parasites are spread to people through the bites of infected *Anopheles* mosquitoes, called "malaria vectors", which bite mainly between dusk and dawn.

There are four types of human malaria:

- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium malariae*
- *Plasmodium ovale*

Plasmodium falciparum and *Plasmodium vivax* are the most common; *Plasmodium falciparum* is the most deadly.

Transmission – Malaria is transmitted exclusively through the bites of female *Anopheles* mosquitoes. The intensity of transmission depends on factors related to the parasite, the vector, the human host, and the environment.

About 20 different *Anopheles* species are locally important vectors around the world. All of the important vector species bite at night. They breed in shallow collections of freshwater like puddles, rice fields, and hoof prints. Transmission is more intense in places where the mosquito is relatively long-lived (so that the parasite has time to complete its development inside the mosquito) and where it prefers to bite humans rather than other animals. The long lifespan, strong human-biting habit of African vector species, and intensity of *Plasmodium falciparum* transmission are the underlying reason why more than 85% of the world's malaria deaths are in Africa.

Human immunity is another important factor, especially among adults in areas of moderate or intense transmission conditions. Immunity is developed over years of exposure, and while it never gives complete protection, it does reduce the risk that malaria infection will cause severe disease. For this reason, most malaria deaths in Africa occur in young children, whereas in areas with less transmission and low immunity, all age groups are at risk.

Transmission also depends on climatic conditions that may affect the abundance and survival of mosquitoes, such as rainfall patterns, temperature and humidity. In many places, transmission is seasonal, with the peak during and just after the rainy season. Malaria epidemics can occur when climate and other conditions suddenly favor transmission in areas where people have little or no immunity to malaria. They can also occur when people with low immunity move into areas with intense malaria transmission, for instance to find work, or as refugees.

Integrated Vector Management (IVM) approach –IVM is a rational decision-making process for the optimal use of resources for vector control. The aim of IVM is to improve the efficiency, effectiveness, and ecological soundness of vector control interventions, and to contribute to achieving national and global targets set for vector borne disease control. To achieve this, vector control programs need to be increasingly based on local evidence, integrate interventions where appropriate, collaborate within the health sector and across other sectors, and actively engage communities (see **Table 1-1**). The process of planning and implementing of IVM includes assessing the epidemiological and vector situation at the country level, analyzing the local determinants of disease, identifying and selecting the vector control methods, assessing needs and resources, developing locally-tailored implementation strategies, and monitoring control efficacy to guide subsequent programmatic decisions (see the WHO Handbook on Integrated Vector Management, 2010).

Table 1-1. Key elements of the IVM strategy

KEY ELEMENTS	DESCRIPTION
Advocacy, social mobilization and legislation	Promotion and embedding of IVM principles in the development policies of all relevant agencies and humanitarian interventions, organizations, and civil society; establishment and strengthening of regulatory and legislative controls for public health; and empowerment of communities.
Collaboration within the health sector and with other sectors	Consideration of all options for collaboration within and between public and private sectors, as well as international organizations and non-governmental organizations; application of the principles of subsidiarity in planning and decision making; and strengthening channels of communication among policymakers, vector-borne disease control program managers and other IVM partners.

Integrated approach	Ensure rational use of available resources through a multi-disease control approach, integration of non-chemical and chemical vector control methods, and integration with other disease control measures.
Evidence-based decision-making	Adaptation of strategies and interventions to local ecology, epidemiology and resources, guided by operational research and subject to routine monitoring and evaluation.
Capacity-building	Development of essential physical infrastructure, financial resources and adequate human resources at national and local level to manage IVM strategies based on a situation analysis.

IVM requires a problem solving approach to vector control, where current and historical field observations, surveillance and situation analysis constitute the basis for a plan of action. An IVM-based process should also be intrinsically cost effective, have indicators for monitoring efficacy with respect to impact on vector populations and disease transmission, and use acceptable and sustainable approaches compatible with local health systems. It should also ensure compliance with local regulations and customs, and reduce the probability of pesticide resistance in mosquitoes. The Malaria Vector Control Program should recognize that malaria is focal and variable in nature—even within a single district or municipality, there may be great differences in transmission risk—and, as a result, there is no single answer to vector control that can be applied in all circumstances.

Insecticide Resistance and Resistance Management – Resistance to insecticides is defined as "*the selection of a heritable characteristic in an insect population that results in the repeated failure of an insecticide product to provide the intended level of control when used as recommended"* based on the definition from the Insecticide Resistance Action Committee. Various mechanisms that enable insects to resist the action of insecticides are grouped into four categories:

Metabolic resistance is the most common form of resistance that occurs in insects. Enzymes produced within insects are often enhanced in resistant strains enabling them to metabolize or degrade insecticides before they are able to exert a toxic effect.

Target-site resistance occurs when the insecticide no longer binds effectively to the site of action within the insect, which results in the insect being unaffected or less affected.

Reduced uptake (cuticular resistance) occurs when the cuticle or digestive tract linings in the insect are modified and prevent or slow the absorption of the insecticide.

Behavioral resistance describes any modification in insect behavior that helps to avoid the lethal effects of insecticides, such as outdoor feeding to avoid indoor insecticide application.

Cross resistance occurs when a resistance mechanism that allows insects to resist one insecticide also confers resistance to compounds within the same class, and may occur between chemical classes. For example, dichlorodiphenyltrichloroethane (DDT) and pyrethroid insecticides are chemically unrelated, but both act on the same target site. Past use of DDT has resulted in a mutation at the target site. These insects that have retained the mutation have some resistance to pyrethroids in addition to DDT.

Resistance occurs when naturally occurring genetic mutations allow a small proportion of the population to resist and survive the effects of the insecticide. By continually using the same insecticides, resistant insects will reproduce, thereby increasing the proportion of resistant individuals in the population. Populations of insects that have never been exposed to insecticides are usually fully susceptible, and resistance genes are rare. Factors that influence resistance development include the following:

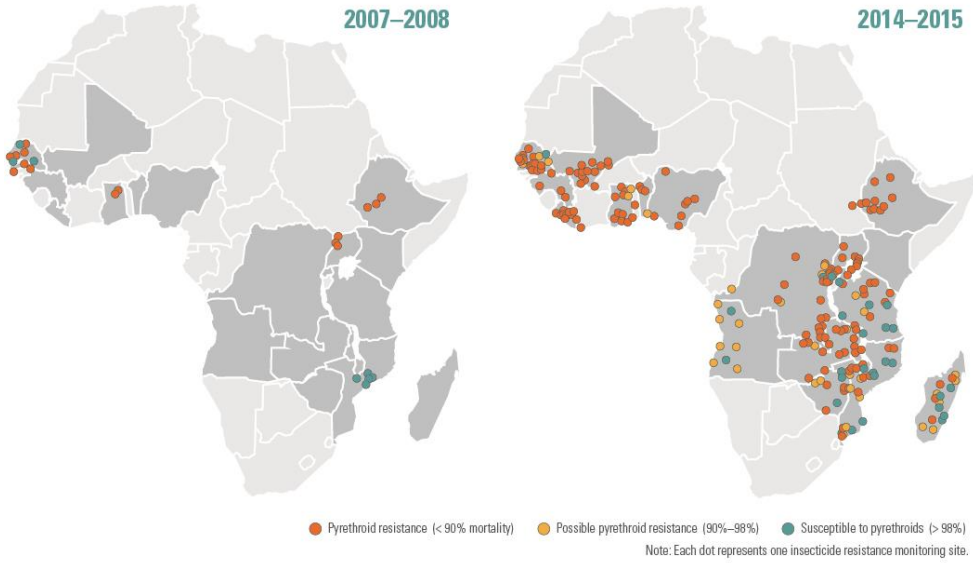
- *Frequency of application* – How often an insecticide is used is one of the most important factors that influence resistance development.
- *Repeated prior exposure to pesticide molecules with similar structures*
- *Dosage and persistence of effect* – An insecticide that remains effective or persists for months or years will

provide selection pressure against many generations.

- *Rate of reproduction* – Insects that have a short life-cycle and high rates of reproduction are likely to develop greater genetic diversity among progenies and a higher rate of resistance more rapidly than species with a lower rate of reproduction.
- *Population isolation* – The goal is often to eliminate all of the population, however the greater the selection pressure that is put on a population, the faster susceptibility may be lost.
- *Environmental factors* – Factors that favor immunity of pest populations contribute to developing strains that retain the ability to resist pesticide effects.

Resistance selection in disease vectors from non-public health pesticides, such as agricultural insecticides, contributes to selection pressure. For example, the initial selection for resistant individuals is often due to application of agricultural insecticides.

Insecticide resistance is one of the most serious threats to malaria control, so resistance management is a key component of IVM. Because recent progress in malaria control has been largely accomplished through a massive increase in vector control through LLINs and IRS, and since both of these prevention measures depend on the ability of insecticides to kill or reduce the lifespan of female mosquitoes, understanding and monitoring insecticide resistance is critical to their continued effectiveness.



Historically, IRS has relied on a limited number of WHOPES-recommended insecticides from only four insecticide classes, and ITNs have relied solely on pyrethroids. In PMI focus countries in sub-Saharan Africa, as of 2015, vector resistance to pyrethroids has been detected in all 19 countries (see **Figure 1-1** below), resistance to carbamates in 16 PMI focus countries, and resistance to DDT in 17 countries. For additional information on insecticide resistance, PMI recently added an "Entomology Monitoring" section to its public website, located at: https://www.pmi.gov/how-we-work/technical-areas/entomological-monitoring. There is a link to the *IRMapper,* which is a tool used to view results from standardized insecticide resistance tests on malaria mosquitoes collected from sites throughout the world, and to which, PMI submits its insecticide resistance data.

Figure 1-1. Expansion of PMI-Supported Insecticide Resistance Monitoring Sites in Africa and Detection of Widespread Pyrethroid Resistance

Although efforts are under way to develop new insect control products that will effectively control insect strains resistant to currently used insecticides, the research and development of these products is an expensive and long-term endeavor. Therefore, detection of insecticide resistance, and use of insecticides for which mosquitoes are susceptible, should be essential components of all national malaria control efforts to protect

and extend the useful life for current insecticides. Effective resistance management requires not only a sound understanding of the vector's biology and the monitoring of vector population, but also the detection, monitoring and consequences of resistance, as well as an understanding of the principles of resistance management.[3] Understanding modes of action of the pesticides is essential for devising a strategy of switching or rotating insecticides.

Insecticide resistance management can, in part, be undertaken using strategic insecticide-based approaches and can take several forms:

- *Rotation* strategies are based on the rotation over time of two or more insecticide classes with different modes of action. The time frame for rotation needs to be sufficiently short to prevent significant levels of resistance to develop.
- *Fine scale mosaics* are the use of spatially separated applications of different compounds against the same insect, such as using two insecticides in different dwellings within the same village.
- *Mixtures* is the co-application of two or more insecticides of different classes and can take the form of a single formulation containing more than one insecticide, two or more insecticide formulations being applied in the same spray tank, or LLINs treated with two or more insecticides.
- *Combination interventions* involve using different insecticide classes applied in different forms within a house (such as using carbamate for IRS and pyrethroid on LLIN).

The USAID Malaria Control Program is currently supporting implementation of insecticide rotations and combination interventions, when possible. This revised PEA evaluates mixtures for both LLINs and IRS, and USAID stands ready to support the approach of using mixtures to combat insecticide resistance once these products are recommended by WHO.

The WHO's *Global Plan for Insecticide Resistance Management* [4] recommends that in areas where IRS is the primary form of vector control, insecticides that share a common target site should not be rotated back-to-back. In addition, the plan recommends that in areas where pyrethroids LLINs are deployed and there is an IRS program, non-pyrethroid IRS should be deployed. Implementation of the *Global Plan for Insecticide Resistance Management* will be more feasible as new, longer-lasting formulations of non-pyrethroid insecticides for IRS and LLINs with non-pyrethroids or synergists become available.

It is critical to note that insecticide resistance has different implications for IRS and larviciding than for LLINs. For IRS and larviciding, it is essential to use insecticides for which mosquitoes are susceptible, and if resistance is detected to an available insecticide, then the insecticide should not be used. For LLINs, on the other hand, which have a physical protective barrier in addition to the insecticide barrier, there is a delayed epidemiological impact when mosquito resistance emerges. Studies document that pyrethroid-treated LLINs continue to provide personal protection in areas with documented pyrethroid resistance.[5] Nonetheless, the ability of insecticide resistance to compromise the epidemiological performance of LLINs is delayed, at best, and it is only a matter of time before pyrethroid resistance begins to undermine the gains that have been made by LLINs in reducing the burden of malaria. USAID remains fully supportive of the collective global efforts to ensure that LLINs, as an intervention, remain fully effective against malaria vectors and protective of at-risk populations through the application of new insecticides to nets. Three new net types are evaluated in this PEA; when WHO issues normative guidance on use of these pyrethroid/non-pyrethroid or pyrethroid plus synergist (see below) nets, USAID will determine if and where best to deploy these LLINs.

Synergists can be defined as compounds that enhance the toxicity of some insecticides by inhibiting the enzymes that metabolize insecticides within the insect. In certain types of resistant insects, synergists can

3 IRAC. Prevention and Management of Insecticide Resistance in Vectors of Public Health Importance. 2010.

4 Available at http://apps.who.int/iris/bitstream/10665/44846/1/9789241564472_eng.pdf?ua=1

5 Lindblade K, Mwandama D, Mzilahowa T et al. A cohort study of the effectiveness of insecticide-treated bed nets to prevent malaria in an area of moderate pyrethroid resistance, Malawi. Malaria Journal 2015, 14:31.

significantly enhance insecticide performance and overcome metabolic resistance. The use of synergists has a valuable place in increasing the activity of certain insecticides on insects with specific resistance mechanisms and prolongs the useful life of those insecticides where resistance is developing. However, there is currently insufficient evidence to determine whether synergists can influence the frequency of resistance genes in a vector population.

Insecticide resistance management can also be undertaken by ensuring implementation of high quality vector control activities to reduce the spread of insecticide resistance. Exposure to sub-lethal application of IRS or poor quality or compromised LLINs (e.g., nets that have been inappropriately stored) may allow mosquitoes with reduced susceptibility to insecticides to survive and pass on the resistance genes. Factors which reduce the efficacy of a vector control program can lead to a shift in the susceptibility status of the mosquito population and should be avoided through informed product choice, effective IRS application, and LLIN distribution and education (IRAC 2010).

1.4 SAFETY OF INTERVENTIONS

The Pesticide Procedures portion of Regulation 216 states that "all proposed projects involving assistance for the procurement or use, or both, of pesticides shall be subject to the procedures prescribed in §216.3(b)(i)." This section fulfills the requirement that "the Initial Environmental Examination for the project shall include a separate section evaluating the economic, social and environmental risks and benefits of the planned pesticide use to determine whether the use may result in significant environmental impact." Included in the PEA are the following factors that are considered throughout this report.

THE USEPA REGISTRATION STATUS OF THE REQUESTED INSECTICIDE

USAID is effectively limited to using active ingredients registered by the USEPA for the same or similar uses. Other pesticides not registered in the United States may be authorized, but only if the USAID program can show that no alternatives are available.

THE BASIS FOR SELECTION OF THE REQUESTED INSECTICIDE

Insecticide selection is based on the following factors: status of WHO recommendation, country registration, duration of malaria transmission season, insecticide resistance levels, availability of insecticide, residual efficacy of insecticide, costs, and safety. All things being equal, a program should choose the active ingredient and formulation that presents the least overall environmental and health human risk.

THE EXTENT TO WHICH THE PROPOSED PESTICIDE USE IS PART OF AN INTEGRATED PEST MANAGEMENT PROGRAM

USAID has adopted integrated vector control as a public health policy because it is the most effective, economical, and safest approach to pest control. The extent of insecticide use will depend on host government approval and the needs of the country specific programs.

THE PROPOSED METHOD OR METHODS OF APPLICATION, INCLUDING AVAILABILITY OF APPROPRIATE APPLICATION AND SAFETY EQUIPMENT

All methods of application will meet state-of-the-science requirements for Best Management Practices (BMPs) including, for example, BMPs for Indoor Residual Spraying (USAID, 2015) and management of LLINs (WHO, 2014; USAID, 2014). Section 2.0 of this document describes the method(s) of application for each malaria control intervention.

ANY ACUTE AND LONG-TERM TOXICOLOGICAL RISK, EITHER HUMAN OR ENVIRONMENTAL, ASSOCIATED WITH THE PROPOSED USE AND MEASURES AVAILABLE TO MINIMIZE RISK

The risk assessment approach described in Section 3.0 represents the core function of this document. The HAARP is used to characterize the potential for adverse effects to workers and residents that may come in contact with insecticides. Section 4.0 presents the risk assessment results, and recommends mitigation options, as appropriate, to minimize exposure.

THE EFFECTIVENESS OF THE REQUESTED INSECTICIDE FOR THE PROPOSED USE

The effectiveness of insecticides chosen is a factor of vector resistance and residual persistence. Monitoring activities will determine the effectiveness (including residual efficacy) in the affected environment.

THE CONDITIONS UNDER WHICH THE PESTICIDE IS TO BE USED, INCLUDING CLIMATE, FLORA, FAUNA, GEOGRAPHY, HYDROLOGY, AND SOILS

This refers to environmental factors that might accentuate the effects of exposure to insecticide, and/or the presence of plants and animals that are of social or economic value. Because the PEA is not developed for specific locations, the affected environment must be addressed in the SEA on a case-by-case basis. Section 3.3 describes a general approach to characterizing environmental risk, primarily focused on larviciding, the intervention with the greatest direct environmental contact.

THE AVAILABILITY AND EFFECTIVENESS OF OTHER INSECTICIDES OR NON-CHEMICAL CONTROL METHODS

Particular vector control interventions are chosen based upon the specific needs and situations (e.g., entomologic, epidemiologic, capacity, etc.) of each country and are most often stipulated in national malaria control strategies. The interventions included in this PEA update have all been shown to be effective in malaria control to different degrees. New insecticides or non-chemical control methods will be considered as new information becomes available.

THE REQUESTING COUNTRY'S ABILITY TO REGULATE OR CONTROL THE DISTRIBUTION, STORAGE, USE AND DISPOSAL OF THE REQUESTED INSECTICIDE

The PMI works within the overall strategy and plan of the host country's National Malaria Control Program (NMCP) and planning and implementation of PMI activities are coordinated closely with each Ministry of Health. Regulatory, legal and institutional settings are discussed in Section 6.0; however, the host country's ability to regulate pesticides should be evaluated on a country-by-country basis in the SEA.

THE PROVISIONS MADE FOR TRAINING OF USERS AND APPLICATORS

USAID recognizes that safety training is an essential component in programs involving the use of insecticides, and provides training recommendations for each intervention.

THE PROVISIONS MADE FOR MONITORING THE USE AND EFFECTIVENESS OF THE INSECTICIDE

Evaluating the risks and benefits of insecticide use should be an ongoing, dynamic process. Recommendations for mitigation and monitoring are including in Section 5.0 of this document.

1.5 NEW TO THIS PEA UPDATE

New pesticides are continuously being developed and researched for malaria vector control. Several new products under the WHO and/or PQ laboratory and/or field-testing and evaluation have been included in this PEA as new options for controlling the malaria vector. Per Regulation 216 section 216.3 (b) requirements, new technologies or insecticides need to undergo an environmental assessment in order to identify the human and environmental risks. Below are the interventions and insecticides that have been reviewed by USAID in this update.

Indoor Residual Spraying

- Chlorfenapyr Suspension Concentrate (SC)
- Clothianidin Water Dispersible Granules (WG)
- Clothianidin and deltamethrin Wettable Powder (WP) in sealed water soluble bag (SB)
- Pirimiphos-methyl Capsule Suspension (CS)

Long-Lasting Insecticidal Nets

- Alpha-cypermethrin and pyriproxyfen on polyethylene
- Alpha-cypermethrin on polyethylene
- Alpha-cypermethrin and chlorfenapyr on polyester
- Permethrin and pyriproxyfen on polyethylene
- Permethrin and piperonyl butoxide on polyethylene
- Deltamethrin on polyethylene

Larvicidal agents (chemical)

- Pyriproxyfen
- Spinosad
- Spinosad 83.3 monolayer
- Spinosad 25 extended release
- Chlorpyrifos
- Diflubenzuron
- Novaluron
- Fenthion
- Methoprene
- Pirimiphos-methyl
- Temephos

Larvicidal agents – biological

- *Bacillus thuringiensis israelensis* (strain AM65-52, 3000 ITU/mg)
- *Bacillus thuringiensis israelensis* (strain AM65-52, 200 ITU/mg))
- *Bacillus thuringiensis israelensis* (strain AM65-52 + *Bacillus sphaericus* strain ABTS-1730; 50 Bsph ITU/mg)
- *Bacillus thuringiensis israelensis* (strain 266/2, $\geq$ 1200 ITU/mg)

Insecticide Treated Clothing (NEW)

- Permethrin

Long-Lasting Insecticidal Hammocks (NEW)

- Permethrin
- Deltamethrin

1.6 USING THIS DOCUMENT

The intended audience and users of this PEA are USAID Washington Technical and Program Officers; USAID Mission Health and Environment Officers; PMI field staff; cooperating country health and environment officials; USAID partners implementing malaria vector control programs; Office of Foreign Disaster Assistance Officers; consultants preparing IEEs, SEAs, and other required approval documents; and the general public. Given the diversity in audiences for this document, as well as the breadth and depth of information presented, we provide a roadmap below that briefly describes the content of each section, and indicates which Annexes provide complementary information.

SECTION 2 – VECTOR CONTROL: ALTERNATIVES AND INTERVENTIONS

This section describes the alternatives and interventions that USAID has implemented or considered for implementation, or is evaluating in this PEA update for malaria vector control. A complete list of products, active ingredients, and status (i.e., EPA and WHO recommendation status) is provided for each intervention. In addition, the PEA summarizes safety concerns, best management practices, and end-of-life issues relevant to the disposition of expired products and waste management. Virtually all of the annexes contain information describing interventions (e.g., spraying rates, insecticide properties), and there are numerous reports and guidance documents available from the WHO and USAID describing BMPs for mixing, application, and disposal of insecticides and insecticide-containing products. However, comprehensive information on insecticide uses, properties, and applications is found in:

- **Annex E** – Pesticide Use and Toxicological Profiles

SECTION 3 – OVERVIEW OF RISK ASSESSMENT METHODOLOGY

This section presents the harmonized approach for human health and the affected environment, respectively. The section begins by providing a useful background that discusses how the PEA risk assessment is structured, and describes the risk paradigm for HAARP that includes Hazard Assessment, Exposure Assessment, and Risk Characterization. The section also presents the generalized risk equation used to estimate the potential noncancer hazard and cancer risk to workers and residents for exposure scenarios relevant to each intervention. Complementary information to this section is found in:

- **Annex F** – Equations Used to Calculate Exposure and Human Health Risk
- **Annex G** – Worked Examples of the Human Health Risk Assessment Process
- **Annex H** – Worked Examples of the Ecological Risk Assessment Process
- **Annex I** – USAID Environmental Procedures (22 CFR 216)
- **Annex P** – Climate Change

SECTION 4 – SUMMARY OF RESULTS

This section summarizes the results of the risk characterization. For each intervention and insecticide, key noncancer hazard and/or cancer risk results are presented along with a description of the exposure scenarios that were evaluated. The section identifies important sources of uncertainty, including bias, discusses data needs relative to sources of uncertainty, and highlights risk assessment conclusions that informed the development of risk mitigation strategies presented in Section 5. Complete results across all exposure scenarios, the full set of input values, and risk equations are provided in:

- **Annex C** – Detailed Risk Assessment Results
- **Annex D** – Physical-Chemical Properties
- **Annex E** – Pesticide Use and Toxicological Profiles
- **Annex F** – Equations Used to Calculate Exposure and Human Health Risk

SECTION 5 – ENVIRONMENTAL MANAGEMENT RESPONSE

The focus of this section is on mitigation of potential safety issues and monitoring of efficacy and safety. For each intervention, the section highlights key updates in progress made and/or policy decisions reached based on previous PEAs' mitigation measures (e.g., biomonitoring for OPs, handling end-of-life LLINs and LLIN packaging, etc.). This section also contains mitigation measures for any insecticide-based intervention. The section is supplemented by information found in:

- **Annex B** – Environmental Compliance Processes for IRS
- **Annex K –** Recommended IRS Mitigation Measures
- **Annex L** – Recommended LLIN Mitigation Measures
- **Annex M** – Recommended Larvicidal Agent Mitigation Measures
- **Annex N** – Organophosphate Biomonitoring Results

SECTION 6 – REGULATORY, LEGAL, AND INSTITUTIONAL SETTING

This section describes the regulatory frameworks and partnerships that form the basis for effective malaria control programs under PMI. Public participation in the host country is emphasized in the development of safe and effective programs that reflect local needs and constraints. Relevant information regarding the selection of interventions and the development of country-specific strategies for malaria vector control is found in:

- **Annex J** – Guidance for Developing SEAs for Malaria Vector Control Programs

SECTION 7 – PUBLIC CONSULTATION

Prior to developing this PEA update, USAID prepared an annotated outline describing the organization and content changes to the document and disseminated, for feedback, to key stakeholders (e.g., key USAID users of the PEA, manufacturers, USEPA, etc.). In addition, USAID posted a draft of the PEA for public comment. This section describes feedback received by USAID in response to these opportunities for comment.

- **Annex A** –Compiled Feedback from the Scoping Exercise
- **Annex O** – Compiled Feedback from the Public Review

SECTION 8 – LIST OF PREPARERS AND REVIEWERS

This section lists contributing authors and principal reviewers.

2.0 VECTOR CONTROL: ALTERNATIVES AND INTERVENTIONS

2.1 ALTERNATIVES CONSIDERED BY USAID

There are two basic alternatives for the USAID Malaria Control Program, either no action, where no interventions would be implemented to control malaria, or the continuation of the USAID Malaria Vector Control Program. The continuation alternative involves

1. the use of existing interventions and insecticides,
2. the adoption of new insecticide products for existing interventions, and
3. the inclusion of new interventions with re-purposed insecticides or new formulations.

USAID has rejected the "no action" option outright because the impacts of no action—disease, human pain and suffering, mortality, reduction in quality of life, and economic losses—are considered antithetic to USAID's mission to support development and the Bureau for Global Health's mission to support a world where people lead healthy, productive lives and where mothers and children thrive.

2.2 USAID-SUPPORTED INTERVENTIONS FOR MVC

As previously stated, USAID supports the scale-up of proven and highly effective malaria control interventions. Currently, USAID relies on two main interventions for malaria vector control: IRS and LLINs, the latter which became commercially available in 2004 when 5.6 million nets were delivered, and have now essentially replaced conventional insecticide-treated nets in Africa.[6] Depending on the vector and country-specific environmental conditions, USAID may utilize larviciding agents for malaria vector control, particularly in the pre-elimination and elimination settings. While insecticide-treated hammocks and clothing have a more limited applicability for malaria control, they have been proven effective in reducing the burden of malaria in forested, mountainous areas where malaria vectors bite outside the house before bedtime. At the present time, there is an inadequate evidence base to support malaria vector control other than by these interventions in most areas of PMI-supported countries.

However, USAID closely collaborates with and supports, in part, the Innovative Vector Control Consortium, whose mission is to advance the research and development of insecticides for public health using a product development partnership model. An overview of new tools in development through the Innovative Vector Control Consortium can be found at: http://www.ivcc.com/creating-solutions/our-work/achievements.

Other technologies under development include shelter materials (e.g., tents, plastic sheeting, etc.), attractive toxic sugar baits, housing improvements, and topical and spatial repellents. These potential tools are being developed by a number of commercial groups, as well as the U.S. Departments of Agriculture and Defense.

Although environmental management is also considered to be a USAID-supported intervention, the development of an environmental management strategy should be determined as part of an SEA, and therefore, only a general description of environmental management options is presented in Annex J (Guidance for Developing SEAs for Malaria Vector Control Programs).

The following section briefly covers the following topics for each intervention

- Background (general information about the intervention)
- Insecticides (insecticides recommended/approved)
- Implementation (deployment of insecticide)
- Safety Considerations (potential risks)

6 Conventional insecticide-treated nets (ITNs), requiring regular retreatment of insecticide, ITNs may still be in use in the Greater Mekong Subregion.

- Best Management Practices (risk mitigation)
- End-of-Life Issues (re-purposing and disposal)

2.2.1 INDOOR RESIDUAL SPRAYING

BACKGROUND

Indoor residual spraying is a commonly used malaria vector control method that is typically implemented by teams of spray operators who spray houses in at-risk localities prior to the rainy season, before heavy rains prompt increases of the *Anopheles* vector population. It is implemented by applying residual insecticides (to which female *Anopheles* mosquitoes have been demonstrated to be susceptible) to the interior walls of houses and other structures. The insecticide remains on the treated surfaces upon which the mosquitoes will rest before or after taking a blood meal. The residual effect of the insecticide is sufficient to kill resting mosquitoes for a period ranging from 3 to 12 months depending on the insecticide, the surface on which it is applied, and local conditions (e.g., temperature, humidity, wall washing patterns, etc.). The objective of IRS programs is to reduce the mean life span of the female mosquito population below the duration required for development of the parasite life phases, and thereby to substantially reduce the population's ability to sustain malaria transmission.

The choice of insecticide class/compound to use in a particular setting should be made with expert consultation and should consider the following factors: insecticide resistance, duration of efficacy versus length of transmission season, and safety, registration status, cost, and availability of product. **Table 2-1** lists IRS insecticides that are either WHO-recommended or undergoing WHO review, and therefore, have been assessed for use in IRS by USAID.

Table 2-1. Insecticides Assessed for Use in IRS by USAID

ACTIVE INGREDIENT[1] (AI) AND FORMULATION	TARGET [AI] G/M^2	PEA IN WHICH ASSESSED	CURRENT PRODUCT NAME(S) [2], STATUS OF WHO AND/OR PQ RECOMMENDATION[3]
Clothianidin WP-SB	0.2	Current	Fludora Fusion, Under review
Deltamethrin WP-SB	0.025		
Chlorfenapyr 240 SC	0.25	Current	Phantom, Under review
Clothianidin WG	0.3	Current	Sumishield, Under review
alpha cypermethrin WP, SC	0.02-0.03	2007	Recommended
Bendiocarb WP	0.1-0.4	2007	Recommended
Bifenthrin WP	0.025-0.05	2007	Recommended
Cyfluthrin WP	0.02-0.05	2007	Recommended
DDT WP	1-2	2007	Recommended
Deltamethrin WP, WG, WG-SG	0.02-0.025	2007	Recommended
Deltamethrin SC-PE	0.02-0.025	2007	Recommended
Etofenprox WP	0.1-0.3	2007	Recommended

ACTIVE INGREDIENT[1] (AI) AND FORMULATION	TARGET [AI] G/M^2	PEA IN WHICH ASSESSED	CURRENT PRODUCT NAME(S) [2], STATUS OF WHO AND/OR PQ RECOMMENDATION[3]
Fenitrothion WP	2	2007	Recommended
Lambda-cyhalothrin WP, CS	0.02-0.03	2007	Recommended
Malathion WP	2	2007	Recommended
Pirimiphos-methyl WP, EC	1-2	2007	Recommended
Pirimiphos-methyl CS	1	Current	Recommended
Propoxur WP	1-2	2007	Recommended

[1]CS = capsule suspension; EC = emulsifiable concentrate; SC = suspension concentrate; SC-PE = polymer enhanced suspension concentrate; WG = water dispersible granules; WG-SB = water dispersible granules in sealed water soluble bags; WP = wettable powder; WP-SB = wettable powder in sealed water soluble bags.

[2]Although the product name is provided in Table 2-1, the USAID IVM PEA approves insecticides for use in IRS by active ingredient(s), formulation, and concentration of active ingredient. Therefore, any new product that has a concentration of active ingredient equal to or less than the concentration of that specific formulation does not need to undergo another USAID risk assessment.

[3] Status as of March, 2015, the most recent summary available from WHOPES.

Note: The USEPA status for all active ingredients listed above is "active" except for bendiocarb and DDT (which have a "cancelled" status).

IMPLEMENTATION

IRS is a method for community protection, and given its mode of action, the highest possible level of coverage (>80% of the homes) is required to achieve the maximum impact of the prevention program on malaria transmission. Achieving this level of coverage and timely spraying in a short period of time before the onset of the transmission season, are crucial to maximize the impact of IRS (WHO IRS Position Statement 2006).

Indoor residual spraying can be effective in almost all of the following settings as long as certain conditions are met:

- In unstable, epidemic-prone malaria transmission areas, IRS will prevent and control epidemics and can be used for the elimination of local transmission of malaria
- In stable-endemic malaria areas with moderately intense but seasonal transmission, IRS can prevent seasonal increase in transmission and reduce levels of infection prevalence and highly seasonal morbidity and mortality
- In stable-hyperendemic areas where very intense seasonal or perennial transmission occurs, IRS, with a higher frequency of application than in above instances, can reduce the level of transmission and reduce levels of infection prevalence, morbidity and mortality

Indoor residual spraying has historically been most effective and most utilized in areas with seasonal malaria transmission. However, with the availability of longer-lasting insecticides, IRS can be effective in perennial transmission settings.

SAFETY CONSIDERATIONS

Insecticide formulations are available as wettable powders, emulsifiable concentrates, capsule suspensions, granules, tablets, and powders in water soluble bags, and need to be mixed prior to application. Consequently, exposures are possible for workers during the spray preparation, actual spraying, and subsequent clean up. In accordance with WHO health and safety regulation, all persons working on IRS must be adequately protected against potential harm due to exposure from pesticides. All persons who may be exposed to pesticides during handling, transportation, storage, use and cleaning of pesticide contaminated materials must wear appropriate personal protective equipment (PPE) in accordance with the PMI IRS BMP Manual (USAID, 2015) and the safety instruction on the product label or material safety data sheet (MSDS).

Residents can be exposed through contact with sprayed surfaces through the dermal path or inhalation upon re-entering homes. However, prior to spraying, residents are instructed to remove and/or protect any food as well as any dishes, utensils, etc., that are normally used for food preparation and eating. Because of this precaution, the 2012 and current PEA update exclude ingestion of food with insecticide residues as a pathway of exposure.

BEST MANAGEMENT PRACTICES

In 2010, USAID, under PMI, developed the first BMP Manual for IRS, which drew on four years of experience in implementing IRS and established a uniform set of BMPs that could be used by any partner or host country implementing IRS. The BMPs were most recently revised in 2015. The IRS BMPs are a compilation of safety standards and practices for the handling, storage, transportation, and use of pesticides used in IRS programs, to minimize the risk for human exposure. It is drawn largely from guidelines from WHO and UNFAO.

The PMI IRS BMPs were developed for all categories of spray personnel, (i.e. supervisors, storekeepers, drivers, washers, and spray operators) and for beneficiaries of the IRS program. It covers the range of activities associated with pesticide use in IRS and is broken down into ten distinct chapters – many with illustrative checklists – as follows:

Table 2-2. Activities Associated with Pesticide Use in IRS

Environmental Assessment	Establishes a uniform approach for the environmental assessment of indoor residual spraying activities intended to ensure compliance with USAID and host country environmental regulations. It also describes the content requirements of the SEA.
Worker and Resident Health and Safety	Provides acceptable safety standards and practices for the handling, storage, transportation and use of pesticides used in IRS as part of the PMI program, to minimize the risk for human exposure. It is drawn largely from guidelines from UNFAO.
Pesticide Storage, Stock Control and Inventory	Provides guidance on the management of pesticide stocks from the point that they have been received in country through the various storage options and eventually to the spray operators and their subsequent return as empty sachets or bottles. Close scrutiny is paid to storage and commodity chain-of-custody to avoid the inadvertent loss or leakage of pesticide stocks. In addition, careful management of storage facilities, stock control and inventory control will minimize the risk of migration into other sectors (e.g., agricultural sector) or the market.
Pesticide Transport	Addresses transport activities involving large quantities of pesticides carried in motorized vehicles, typically trucks or pickup trucks, but also boats. Frequently, because of the nature of the program, these pesticides are being transported to remote rural areas, over poor roads, where supervision and assistance becomes more difficult in the event of an accident.

Spraying Techniques	Provides appropriate safety standards and practices for spraying activities and addresses best practices for appropriate equipment, preparing the pesticide mixture, spraying techniques and cleaning spray pump and nozzles.
Effluent Waste Disposal	Addresses site considerations, standard design and construction, proper use, and decommissioning protocols for the IRS effluent cleaning and disposal facilities. ***New feature in 2015 BMP: Introduction of mobile soak pits****
Solid Waste Disposal	Provides acceptable safety standards and practices for the storage and disposal of solid wastes generated during IRS operations.
Spill Response	Provides acceptable safety standards and practices for responding to pesticide spills in the event of an accident.
DDT Special Considerations	Provides acceptable safety standards and practices for the handling, storage, transportation and use of DDT in IRS as part of the PMI program, to minimize the risk of human exposure.
Water Crossing	***New chapter in 2015 BMP**** Provides protocol for methods that are to be used for transporting pesticides across water.

The BMP Manual can be accessed through the following link on the PMI website: https://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/best-practices-indoor-residual-spraying-feb-2015.pdf.

INCIDENT REPORTS

If an environmental or human health incident does occur from a result of an IRS campaign, the COR/AOR will alert, in a timely fashion, relevant staff, including but not limited to their respective leadership and environmental officers. It is a best practice for CORs and/or AORs of IRS projects to consult with environmental officers and determine a protocol for incident reporting (timeline, needed documentation, etc.).

END-OF-LIFE ISSUES

End-of-life issues for IRS refer to any activity involved in handling insecticide residuals that will not be used in spraying. This includes wash water produced by cleaning equipment (e.g., sprayers, PPE), wastewater from washing overalls or gloves, pesticide containers, or expired pesticides. Solid wastes produced during spray activities include packaging, damaged PPE, or materials that become contaminated from accidental spills or leaks. Section 5 contains mitigation measures for addressing liquid and solid insecticide-contaminated waste.

2.2.2 LONG-LASTING INSECTICIDAL NETS

BACKGROUND

Insecticide-treated mosquito nets are a highly effective means of preventing infection and reducing malaria transmission. Polyethylene and polyester are the most common materials used for mosquito nets given their relative strength and durability, but polypropylene has been used in the past. Insecticide is incorporated within the net's polyethylene fibers during manufacture, for slow release over a sustained period of time. For polyester nets, the resin coating process for the insecticide is intended to control the bioavailability of the active ingredient, ensuring that surface concentrations are depleted very slowly. In both cases, the concentration on the surface of the material may be depleted by physical contact, washing, or decomposition in sunlight.

To date, only pyrethroid insecticides have been recommended for use in LLINs due to the combination of safety and repellency indicative of pyrethroids, high knock down effect, and mosquito irritancy at low dosages. Unlike conventional insecticide-treated nets (ITNs), LLINs maintain effective levels of insecticide for an average of 3 years[7] of recommended use under field conditions, and for at least 20 standard WHO washes in the laboratory conditions (WHO 2006). The WHO Global Malaria Program has called upon national malaria control programs and their partners supporting conventional ITN activities to purchase only LLINs.

USAID Malaria Control Program's procurement policies require that USAID only procure LLIN products recommended by WHO. As environmental requirements are one factor of many in USAID's LLIN procurement policies, please refer to the following link for the full set of procurement specifications: https://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/itn_procurement_specifications.pdf.

Table 2-3. Insecticides Assessed for Use in LLINs by USAID

ACTIVE INGREDIENT (AI) OR SYNERGIST, AND TREATMENT	MAXIMUM ACTIVE INGREDIENT MG/M^2 ASSESSED IN PEA	PEA IN WHICH ASSESSED	CURRENT PRODUCT NAME(S)[1], ACTIVE INGREDIENT(S) (MG/M^2), STATUS OF WHO AND/OR PQ RECOMMENDATION[2]
Alpha-cypermethrin, polyester	100	Current	Interceptor G2, 100 / 200, Under review
Chlorfenapyr, polyester	200		
Permethrin, polyethylene	800	Current	Olyset Duo, 800 / 400, Under review
Pyriproxyfen, polyethylene	400		
Alpha-cypermethrin, polyethylene	225	Current	Royal Guard, 225 / 225, Under review Veeralin, 216/79.2, Interim DuraNet Plus, x/x, Under review
Pyriproxyfen, polyethylene	225		
Permethrin, polyethylene	800	Current	Olyset Plus, 800 / 400, Interim
Piperonyl butoxide, polyethylene	400		
Alpha-cypermethrin, polyethylene	261	Current	DuraNet, 261, Recommended MAGNet, 261, Recommended MiraNet, 180, Interim Royal Sentry, 261, Recommended
Permethrin, polyethylene	1000	2012	Olyset, 1000, Recommended
Deltamethrin, polyethylene	76	Current	Panda Net 2.0, 76, Interim
Deltamethrin coated on polyester and on polyethylene	115	2012	PermaNet 3.0, 115 / 25 g/kg, Interim

7 Depending on conditions and net material, the viable life of the net may vary.

ACTIVE INGREDIENT (AI) OR SYNERGIST, AND TREATMENT	MAXIMUM ACTIVE INGREDIENT MG/M^2 ASSESSED IN PEA	PEA IN WHICH ASSESSED	CURRENT PRODUCT NAME(S)[1], ACTIVE INGREDIENT(S) (MG/M^2), STATUS OF WHO AND/OR PQ RECOMMENDATION[2]
roof			
Piperonyl butoxide incorporated into polyethylene (roof)	25 g/kg		
Deltamethrin, polyester	80	2012	DawaPlus 2.0, 80, Interim PermaNet 2.0, 55, Recommended Yahe, 55.5, Interim Yorkool, 55, Recommended
Alpha-cypermethrin, polyester	200	2012	Interceptor, 200, Recommended SafeNet, 200, Recommended

[1] Although the product name is provided in Table 2-3, the USAID IVM PEA calculates risk by factoring in active ingredient, concentration of active ingredient, and material type. Therefore, any new product that has a concentration of active ingredient equal to or less than the concentration of those specified above (and the same netting material) does not need to undergo a USAID risk assessment.

[2] Status as of April, 2016, the most recent summary available from WHOPES.

IMPLEMENTATION

The WHO calls for countries to reach and maintain universal coverage of LLINs for all individuals living in malaria endemic areas, with a specific target that at least 90% of households with a pregnant woman and/or children under five years of age own at least one ITN. Universal coverage is operationally defined as one ITN for every two individuals. There are two key distribution channels. Free-standing, mass distribution campaigns are successful in rapidly and equitably achieving universal coverage. A mix of routine distribution channels – including antenatal care clinics, expanded programs on immunization clinics, schools and/or community-based distributions – is then needed to maintain universal coverage and address those missed by the campaign, new entries to the population by birth or immigration, and physical deterioration of existing nets.

While rapid scale-up of LLIN distribution in Africa represents an enormous public health achievement, it also represents a formidable challenge for the future in ensuring that the high levels of coverage are maintained. For example, experience has shown the communication strategies that accompany LLIN distribution are not always effective in educating communities with regard to the importance of proper hanging, use, and maintenance of LLINs. In addition, with a lifespan of roughly three years for the current generation of LLINs, it is critical to set up sustainable mechanisms for their replacement.

SAFETY CONSIDERATIONS

The replacement of conventional ITNs with LLINs has had two significant impacts on the potential risks to workers and residents. First, because the LLINs are factory treated, the exposure scenarios associated with dipping are no longer relevant. In addition, the incorporation of insecticides into polyethylene fibers greatly reduces the potential for exposure through direct contact. The same net characteristics that control the slow release of insecticide also serve to reduce exposures. Nevertheless, given the amount of time in contact with LLINs during sleeping, and the need to wash the nets periodically, resident exposures are likely and thus are evaluated in this PEA update.

BEST MANAGEMENT PRACTICES

As previously mentioned, there are two main kinds of LLINs – polyester nets that are resin coated with the insecticide, and polyethylene nets where the insecticide is incorporated into the fiber. Pyrethroids bind strongly to the fabric and even when washing with soap and water, only part of the insecticide is removed. The nets regain efficacy (regenerate) within 24 hours of washing (up to 15 days after washing in tropical climates), to allow time for the pesticide to recharge the surface. Some manufacturers recommend to air out new nets for 24 hours before initial use. It is recommended to wash the net gently in soapy, cold water without prolonged soaking, and not more than four times per year (WHO 2002). Nets should not be washed in or near water bodies and water used for washing and rinsing the net should be disposed of in a latrine or on the ground, away from homes and animals (WHO 2002).

END-OF-LIFE ISSUES

Nets that are no longer viable (e.g., holes are too large to mend) are often reused within the household as curtains, eave screens, and other uses for pest control, all of which can be considered viable and safe. However, some percentage of LLINs may be re-purposed in ways that could increase exposure to pyrethroids, such as fishing. PMI does not consider use of LLINs for fishing an appropriate repurposing of bed nets. The WHO has published recommendations for the safe use and disposal of expired LLINs[8] (WHO 2014). Section 5 contains those recommendations and summarizes the studies, literature reviews, and discussions to date on end-of-life issues associated with LLINs.

2.3.3 LARVICIDING

BACKGROUND

Larviciding is the general term for treating standing water with different agents to prevent immature mosquitoes in the larval and/or pupal stage from becoming adults. Larvae often are concentrated within defined water boundaries, are immobile, and have limited ability to disperse. Most species spend the majority of their life cycle in the larval stage where they are highly susceptible to both predation and control efforts.

Larviciding is often used in conjunction with environmental management interventions that, taken together, reduce the surface water area available for mosquito breeding and create "kill zones" for larvae. Naturally, knowledge of the local ecology and biology of the target species is necessary to develop a cogent control strategy involving larviciding; the timing, dose, and method of application (e.g., air dispersal, boat delivery) will dictate the success of the strategy. Three basic types of larvicidal agents are available as interventions:

Chemical insecticides – This category of larvicide includes active ingredients that are toxic to larvae, or affect biological functions such as growth. Insecticide growth regulators affect the physiology of morphogenesis, reproduction and embryogenesis of insects.

Microbial insecticides – This category of larvicide are derived from bacteria that occur naturally in soil and aquatic systems, and produce a toxin that typically affects the gut, resulting in mortality to the larvae. The treatment is relatively fast acting, and typically lasts only a few weeks.

Surface oils and monomolecular films – This category of larvicide acts by either physically suffocating the larvae (surface oil slick), or reducing the surface tension of the water so that emerging adult mosquitoes become disoriented and drown (surfactant). These compounds have very low toxicity and depend on timing to be effective.

While the USAID Malaria Control Program is not currently procuring larvicides, it has historically only procured larvicides recommended by WHO. Table 2-4 lists the larvicides evaluated in this PEA. Note that potential health risks related to the biological larvicide *Bacillus thuringiensis* are evaluated in a descriptive manner.

[8] http://www.who.int/malaria/publications/atoz/who-recommendation-managing-old-llins-mar2014.pdf

Table 2-4. Insecticides Assessed for Use in Larviciding by USAID

ACTIVE INGREDIENT[1] (AI)	MAXIMUM ACTIVE INGREDIENT MG/M^2 ASSESSED IN PEA	PEA IN WHICH ASSESSED	CURRENT PRODUCT NAME(S) [2], STATUS OF WHO AND/OR PQ RECOMMENDATION[3]
Diflubenzuron DT, GR, WP	10	Current	Dimilin
Novaluron EC	10	Current	Novaluron 10%
Pirimiphos-methyl EC	50	Current	Pirimiphos-methyl 300 CS
Spinosad DT, EC, GR, SC	50	Current	Spinosad
Spinosad DT	50	Current	Spinosad 83.3 monolayer
Spinosad GR	40	Current	Spinosad 25 extended release
Pyriproxyfen GR	5	Current	Sumilarv 0.5
Chlorpyrifos EC	2.5	Current	-
Fenthion EC	11.2	Current	-
Temephos EC, GR	11.2	2007	Abate, ProVect
Methoprene EC	3	2007	Altosid
Bacillus thuringiensis israelensis, strain AM65-52 (200 ITU/mg) G	1250	Current	VectoBac
Bacillus thuringiensis israelensis, strain AM65-52 (3000 ITU/mg) WG	46.9	Current	VectoBac
Bacillus thuringiensis israelensis, strain AM65-52 + *B. sphaericus* strain ABTS-1743; 50 Bsph ITU/mg G	1250	Current	VectoMax
Bacillus thuringiensis israelensis, strain 266/2 (>1200 ITU/mg) SC	4 mL/m^2	Current	-

[1] DT = tablet for direct application; GR = granule; EC = emulsifiable concentrate; WG = water-dispersible granule; WP = wettable powder.

[2]Although the product name is provided in Table 2-4, the USAID IVM PEA calculates risk by factoring in active ingredient, formulation, and concentration of active ingredient. Therefore, any new product that has a concentration of active ingredient equal to or less than the concentration of those specified above does not need to undergo a USAID risk assessment.

[3] Status as of April, 2016, the most recent summary available from WHOPES.

Note: The USEPA status for all active ingredients listed above is" active" except for temephos, which was voluntarily cancelled by the Registrant.

IMPLEMENTATION

Surveys should be carried out to prior to larviciding to identify priority breeding sites, as these will vary considerably depending on the species and environment. Larval habitats can be small, widely dispersed, and transient, and it can be very difficult to predict when and where breeding sites will form, and to find and treat them before the adults emerge. Community-based microbial larviciding interventions have shown to be effective when planned appropriately and used in conjunction with other interventions such as ITNs (Maheu-Giroux and Castro, 2013). However, there are very few studies to support the efficacy of this approach in sub-Saharan Africa. Therefore, larviciding generally is recommended only for vectors that tend to breed in permanent or semi-permanent water bodies that can be identified and treated (i.e., few, fixed, and findable), and where the density of the human population to be protected is sufficiently high to justify the treatment of all breeding places at relatively short intervals. Modified sprayers can be used for effective application of liquid or granule larvicides. The interval for re-treatment with chemical and bacterial larvicides is usually 7-10 days, but can be longer for standing clear water or with treatment at higher dosages.

SAFETY CONSIDERATIONS

Depending on the method of application, workers may be exposed during the preparation of the chemical larvicides as well as while applying to standing water (e.g., using sprayers). Residents may be exposed via contact and/or ingestion of waters with residuals from chemical larviciding. Microbial larvicides are classified by the USEPA as General Use Pesticides (GUPs) and are considered safe for humans, non-target organisms, and the environment. The toxins produced by *B. sphaericus* and *B. thuringiensis* are not activated in the human gut, and these larvicides typically do not last more than a 1-3 weeks in the environment. Therefore, these microbial larvicides are not considered to pose risks to humans.

Plant-based surface oils and films used in larviciding are essentially non-toxic to humans, and petroleum-based surface oils are not recommended due to the potential toxicity of degradation products. Care should be taken with respect to environmental impacts even for plant-based products because beneficial aquatic plants and animals can be adversely affected through the interactions with surface biology and chemistry.

BEST MANAGEMENT PRACTICES

Chemical larvicides should be handled according to manufacturer's safety instructions available on the MSDS. Recommended dosages of insecticides should not be exceeded, particularly when applied to water bodies that might be used by humans or domestic animals, or that contain wildlife of social and/or importance (WHO 2006).

END-OF-LIFE ISSUES

Given the relatively rapid breakdown of larvicides in the environment, no end-of-life issues are anticipated.

2.2.4 INSECTICIDE TREATED CLOTHING

BACKGROUND

Insecticide-treated clothing has been used for over 20 years by the military to protect soldiers from diseases carried by insect vectors. Factory-treated clothing and treatment kits are available from a variety of vendors, including camping outfitters, hunting and sporting goods stores, and on-line retailers. Permethrin was first registered with the USEPA in 1990 as a repellent on clothing for the military. In 2003, it was first registered for factory-treated clothing products that could be sold to consumers. There are a number of studies demonstrating the efficacy of permethrin-treated clothing in preventing the transmission of disease, including malaria (Kimani et al., 2006) and dengue (e.g., DeRaedt Banks et al., 2015).

INSECTICIDES

Permethrin is the only insecticide that is USEPA-approved for treated clothing, and is the only insecticide under consideration by USAID for this intervention. Permethrin is a broad spectrum, non-systemic, synthetic pyrethroid insecticide that binds well to fabric, has low volatility, and is absorbed poorly through the skin.

IMPLEMENTATION

Unlike IRS and LLINs, USAID supports the use of insecticide-treated clothing in more limited settings – specifically, to protect migrant workers in countries in the Greater Mekong Subregion who work in forested

areas. For best results, studies suggest that the treated clothing cover as much skin as possible; consequently, treated long-sleeved shirts and pants are recommended (Orsborne et al., 2016). In addition to factory-treated clothing, treatment kits and permethrin sprays are also used to treat clothing. The treatment kits typically involve soaking in an aqueous emulsion, and are designed to produce little or no waste. Clothing is soaked in the emulsion, and then air-dried to facilitate the adherence process to clothing fibers. Garment performance is similar for soaking and spraying applications, as vendor claims indicate that the repellent should continue to work up to six weeks and six washings. In contrast, factory-treated clothing can last up to 70 washings according to some manufacturers (e.g., InsectShield).

SAFETY CONSIDERATIONS

The USEPA completed a comprehensive human health risk assessment for all registered uses in 2006 in support of the reregistration process. In 2009, the USEPA evaluated several factory-treated exposure scenarios, including short-term and long-term cancer risks to adults, children, and toddlers wearing permethrin-treated clothing. The risk assessment included toddler object-to-mouth activity on factory-treated clothing. None of the exposure scenarios that the USEPA evaluated were considered to pose significant immediate or long-term risk to people wearing factory treated clothing because (1) the amount of permethrin in clothing is very low, (2) the level of exposure consistent with recommended uses is low, and (3) permethrin is poorly absorbed through the skin.

BEST MANAGEMENT PRACTICES

Clothing that is factory-treated with permethrin includes a pesticide use label, consistent with regulatory requirements. The pesticide use label on clothing is generally attached to the outside of the clothing, and provides directions and precautions regarding the use and washing of treated clothing. For example, although only small amounts of permethrin in treated clothing come off in the wash, most vendors recommend washing treated clothing separately from non-treated clothing, particularly clothing worn close to the skin (e.g., underwear). Similarly, permethrin sprays are only recommended for outer clothing. Other BMPs for permethrin treated clothing include

- Do not apply permethrin directly to skin
- Do not apply spray to clothing while wearing
- Apply sprays in well-ventilated areas
- Hang fabrics outdoor to dry after treating (soak or spray).

END-OF-LIFE ISSUES

It is unlikely that there will be significant end-of-life issues for permethrin-treated clothing given the relatively low amount of permethrin in treated clothing, the level of adherence of permethrin to clothing fibers, and the intrinsic value of clothing (treated or untreated). However, it is important to include precautionary advice for adults/parents to be aware not to let infants (especially those teething) chew or suck on treated clothing.

2.2.5 LONG-LASTING INSECTICIDAL HAMMOCKS

BACKGROUND

Synthetic pyrethroids (e.g., permethrin and deltamethrin) are approved for LLINs and, because of their safety and repellency, they are also an appropriate choice for hammocks. Like permethrin-treated clothing, treated hammocks are sold by retailers such as hunting and sporting goods stores, and can be combined with LLINs for more complete coverage. Factory-treated hammocks have many of the same characteristics of LLINs and permethrin-treated clothing.

INSECTICIDES

Both permethrin- and deltamethrin-treated hammocks have been included in the risk assessment conducted under this PEA update.

IMPLEMENTATION

The most significant use for insecticide treated hammocks is personal protection against the bites of forest malaria vectors in Southeast Asia (e.g., Thang et al., 2009, Sochantha et al., 2010). This intervention can be

particularly effective in remote hot and humid forest areas where there are outdoor-biting vectors and residents regularly sleep outdoors. Therefore, similar to insecticide-treated clothing, USAID has targeted LLIHs to migrant workers whose employment requires overnight stays in forested areas.

SAFETY CONSIDERATIONS

The USEPA's comprehensive human health risk assessment and updates conducted for permethrin-treated clothing is applicable to treated hammocks. The treated clothing exposure scenarios should, generally, be more protective for treated hammocks because the contact duration should be less for hammocks than for clothing.

As with LLINs, LLIHs are factory treated, eliminating exposure scenarios associated with preparation and dipping. In addition, the incorporation of insecticides into polyester fibers greatly reduces the potential for exposure through direct contact. The same net characteristics that control the slow release of insecticide also serve to reduce exposures.

BEST MANAGEMENT PRACTICES

Hammocks that are factory-treated with pyrethroids will include a pesticide use label, consistent with regulatory requirements. The pesticide use label provides directions and precautions regarding the use and washing of treated hammocks. As with treated clothing, treated hammocks should be washed separately from non-treated articles.

Pyrethroids bind strongly to the polyester fabric and even when washing with soap and water, only part of the insecticide is removed. As with nets, hammocks regain efficacy (regenerate) within 24 hours of washing (up to 15 days after washing in tropical climates), to allow time for the pesticide to recharge the surface. Best management practices for nets should be followed for hammocks. For instance, the WHO recommends washing the net gently in soapy, cold water without prolonged soaking, and not more than four times per year (WHO 2002). Hammocks should not be washed in or near water bodies and water used for washing and rinsing the hammock should be disposed of in a latrine or on the ground, away from homes and animals (WHO 2002).

END-OF-LIFE ISSUES

Significant end-of-life issues for treated hammocks are unlikely given the relatively low amount of insecticide in treated material.

3.0 RISK ASSESSMENT METHODOLOGY

As discussed in Section 1.4, risk assessment is intended to support the decision-making process regarding the safety of interventions that are currently included or proposed as part of an integrated vector management strategy. Risk assessment methodologies should be transparent, reflect best practices across the USEPA and WHO and, most importantly, be "fit for purpose." Within the context of the Malaria Control Program, "fit for purpose" means that the methodology should be intentionally conservative to screen out active ingredients and/or products that pose unacceptable safety risks to human health or cause significant damage to the environment. For example, the methodology includes a "lax scenario" intended to represent situations in which PPE is not worn, and/or BMPs are not consistently implemented. Including both lax and guideline scenarios ensures that the risk assessment covers the full range of field operations, and provides USAID with the operational flexibility to develop mitigation strategies that address variability in safety compliance.

The methodology described in this section draws on the methods described in previous USAID reports on IVM programs, the WHO's Generic Risk Assessment Models (implemented for IRS, ITNs, and larviciding), and guidance documents and standard operating procedures published by the USEPA. As new interventions and formulations are introduced, USAID continues to develop methods and appropriate data to characterize the potential for adverse effects on human health and the environment. Reports and documents that were most influential in developing in HAARP included, for example

- Integrated Vector Management Programs for Malaria Vector Control (USAID, 2007)
- 2012 Integrated Vector Management Programs for Malaria Vector Control Programmatic Environmental Assessment (USAID, 2012)
- Standard Operating Procedures for Residential Pesticide Exposure Assessment (USEPA, 2012)
- Framework for Human Health Risk Assessment to Inform Decision Making (USEPA, 2014)
- Region 4 Ecological Risk Assessment Supplemental Guidance Interim Draft (USEPA, 2015)
- Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (USEPA, 2015)
- Risk Assessment Guidance for Superfund, Parts A-F
- WHO Generic Risk Assessment Model for IRS (2011), ITN (2012), and Larviciding (2011)

This section is intentionally succinct to ensure that the reader will have adequate information to understand the methodology and understand the basis for recommendations. However, the documents listed above can be consulted for additional discussions on data sources, risk assessment theory, and the application of these techniques as part of a broader risk management framework.

3.1 RISK ASSESSMENT FUNDAMENTALS AND THE PEA UPDATE

The fundamentals described below are not intended to serve as a primer on risk assessment; there are numerous reports and guidance documents (see above) as well as texts and journal articles that provide much more rigorous treatment of this topic. Instead, this discussion is intended to paint the risk assessment landscape in terms of the approaches that were available to USAID to characterize health and environmental risks associated with malaria vector control interventions. These fundamentals served to inform the development of the HAARP, and provided useful criteria to ensure that the methodology was fit for purpose. Under each fundamental sectopm, we highlight salient features of the HAARP to facilitate an understanding of the approach, and to provide the context with which to interpret the risk assessment results.

Definition of Risk – By most definitions, risk is described as a function of severity and probability, with the severity related to adverse effects (e.g., health endpoints such as neurotoxicity) that are considered material to a specific decision, and the probability related to factors that determine whether adverse effects *could* occur (e.g., dermal contact with insecticide). Low severity and low probability are typically interpreted as indicators of low risk and not of concern; conversely, high severity and moderate–high probability are considered indicators of high risk (i.e., the risk warrants concern and is relevant to the decision).

The severity of potential adverse effects in **HAARP** is represented by human health benchmarks and by ecological screening criteria, respectively. If exposure exceeds these "reference values," then the results are interpreted as an increased probability that the use and application of a particular insecticide or product will not be safe. Probability of effect, in this scheme, does not refer to a statistical probability; rather, it recognizes that the quantitative risk estimates are indicators of potential effects.

Approaches to Assess Risk – The determination of severity and probability can be done qualitatively, semi-quantitatively, or quantitatively depending on the goals for the assessment (e.g., the decision problem) and the quality of the information available. Risk assessors often use a tiered framework that combines these approaches, using qualitative information initially to frame the risk problem, and progressing from very simple semi-quantitative techniques to more complex quantitative schemes, often involving mathematical models. This progression supports productive interactions between the risk manager and risk assessor, and provides information that can be used prioritize further data collection.

The **HAARP** begins with an assessment of a potential hazard – collecting and evaluating data on the insecticide and intervention. Based on that review, it is determined whether or not to perform risk calculations. For example, with respect to permethrin-treated clothing, there was sufficient information available to determine, semi-quantitatively, that this intervention does not pose significant safety risks.

Quantifying Risk – For risk assessments that rely on some form of quantitative expression of risk, mathematical models are required. These include statistical models typical of retrospective risk assessments, as well as predictive, mechanistic models that use first principles to predict the future state of the system based on known or assumed relationships. In a retrospective risk assessment, data are available with which to quantify the relationship between risk factors and outcomes. For example, epidemiological studies on occupational exposures to industrial chemicals can produce risk ratios based on the health outcomes observed at specific levels of exposure. In contrast, in the absence of suitable study data, a predictive risk assessment is conducted to "forecast" whether or not combinations of risk factors will produce adverse effects that exceed levels of concern. Predictive risk models tend to be mechanistic in the sense that they generally represent scientific processes to arrive at the risk forecast (rather than fitting statistical models to existing data sets).

Epidemiological data were generally unavailable for the purposes of characterizing potential risks for most or all exposures to insecticides considered in this PEA update. Therefore, we used predictive risk models in **HAARP** to calculate potential risks to health and, for larvicides, the environment. The models quantify risk using data on insecticides (e.g., toxicology), general information on pesticide handling (e.g., unit exposures), and worker and resident characteristics (e.g., body weight).

Uncertainty and Variability – Naturally, with any mathematical model, there is uncertainty with respect to the form of the equation (i.e., does the equation adequately represent the risk problem). In addition, there is uncertainty and variability associated with the input parameter data. In virtually any risk assessment, there is measurement uncertainty (i.e., uncertainty that *could* be reduced by collecting more data) and there is variability (i.e., the variance in the input parameter that can only be represented, not reduced). Probabilistic modeling techniques can be used to better understand the impact of uncertainty and variability on the risk estimates and, minimally, provide a more precise expression of risk based on the distribution of risk estimates. Alternatively, deterministic models use a single value for each parameter, producing a point estimate rather than a distribution of risk. Conservative (i.e., overstating risk) input values are typically used to ensure that a deterministic result will not underestimate the potential risk.

Decision Context – Lastly, and sometimes overlooked, is the importance of understanding the risk management decision in developing the risk assessment approach as well as in interpreting the results of the risk assessment. This decision context frames the risk problem and informs the choices with respect to the

previous criteria. In essence, the decision context answers the question "how accurate do the risk estimates need to be to support the decision-making process?" For safety decisions, the risk manager often needs to have high confidence that the risk results do not underestimate the actual risk, but does not need to have an accurate expression of the risk. Put another way, the risk manager may be most interested in a plausible upper bound of the potential risk rather than the most accurate expression of the actual risk. This approach is typical of screening risk assessments that are designed to represent this upper bound while, at the same time, avoiding a level of conservatism that the risk information is not meaningful.

In developing the **HAARP**, we recognized that the purpose of the risk assessment was to ensure that any potentially serious safety issues were identified. However, we also recognized that methods developed by the USEPA and WHO needed to brought into alignment, supporting efficiency, transparency, and consistency in risk assessments of new insecticides and products. The **HAARP** bridges these methods by creating a conservative approach to characterize the *potential* risks to human health and the environment, and providing context needed to understand and interpret the quantitative risk results.

3.2 HUMAN HEALTH RISK ASSESSMENT

From the definition of risk presented in Section 3.1, all activities in a risk assessment can be organized around (1) understanding the severity of an effect (i.e., how bad can the effect be), (2) estimating the probability that the effect will occur (i.e., how likely is it), and (3) combining severity and probability into an expression of risk (i.e., cancer risk or noncancer hazard). This organization tracks very well with the risk assessment paradigm[9] developed by the WHO that consists of:

Hazard assessment – assess the ***hazard*** associated with the insecticide and insecticide-containing products, identifying critical health endpoints of concern (e.g., neurotoxicity) and scientifically supported health benchmarks

Exposure assessment – determine the potential for ***exposure*** to the chemical through different exposure pathways (how the insecticide and person arrive at the same location in time and space) and routes of exposure (how a person comes in contact with an insecticide)

Risk Characterization – use the data gathered during the Hazard Assessment and Exposure Assessment to develop quantitative estimates of noncancer hazard and noncancer risk for each exposure scenario for each active ingredient; interpret the quantitative and qualitative information to ***characterize*** the ***risk*** of adverse health effects

The ability of a pesticide used in malaria vector control to elicit adverse health effects depends on the route of exposure (i.e., ingestion, inhalation, or dermal), the frequency and duration of exposure (i.e., acute, subchronic, or chronic) the toxicity of the insecticide (which may vary by route and duration of exposure), and the sensitivity of the exposed individual. Nevertheless, the human health risk assessment process can be broken down into two very basic steps. First the average daily systemic dose of an active ingredient (ai) to an individual is calculated as a function of the

- insecticide ***concentration*** in the product/medium (e.g., mg ai/ml)
- the rate of ***contact*** that person has with the insecticide per day (e.g., ml/day)
- the ***absorption*** given the exposure route (e.g., inhalation - unitless)
- the ***body weight*** for that receptor (e.g., kg of an average adult)

9 The WHO paradigm is consistent with USEPA risk assessment paradigm; the primary difference is that the WHO has combined Hazard Identification and Dose Response analysis into Hazard Assessment. For the purposes of harmonization, USAID elected to use the simpler WHO paradigm.

Expressed mathematically, the average daily systemic dose is given by

$$Systemic\ Dose\ = \frac{Concentration\ \left(\frac{mg\ ai}{unit}\right) \times Contact\ Rate\ \left(\frac{unit}{day}\right) \times Absorption}{Body\ Weight\ (kg)}$$

After the average daily systemic dose has been calculated for an insecticide, that value is compared to the corresponding human health benchmark that represents an acceptable dose for human receptors. For noncancer endpoints, this comparison produces a Hazard Quotient (HQ) as the risk assessment metric, which is simply the ratio of the systemic daily dose to the health benchmark.

$$Hazard\ Quotient = \frac{Systemic\ Dose\ \left(\frac{mg}{kg \cdot day}\right)}{Health\ Benchmark\ \left(\frac{mg}{kg \cdot day}\right)}$$

Hazard quotient values greater than 1 suggest *some* potential for adverse noncancer effects; the higher the HQ, the greater the potential for adverse effects. Given the overall conservatism of the HAARP, HQ values below 1 indicate a very low potential for any adverse effect.

For cancer endpoints, the calculation of average daily systemic dose is identical to the equation for noncancer effects. However, the risk metric is the Incremental Lifetime Cancer Risk (ILCR), which is simply the product of the systemic dose (amortized over an individual's lifetime) and the cancer slope factor

$$ILCR = Systemic\ Dose\ \left(\frac{mg}{kg \cdot day}\right) \times Cancer\ Slope\ Factor\ \left(\frac{mg}{kg \cdot day}\right)^{-1}$$

The ILCR values are expressed in terms of the probability of an individual contracting cancer over the lifetime based on exposure to a cancer-causing agent. Although different governmental agencies (domestic and international) establish different ranges for levels of concern, a cancer risk above 1 in 10,000 is generally regarded as unacceptable from a regulatory standpoint. Relative to this threshold, the higher the ILCR, the more significant the potential risk of cancer.

Section 3.2.1 provides an overview of the basic steps in the WHO risk assessment paradigm. The paradigm is described in sufficient detail to understand what information is required, how risks are quantified and characterized, and how the information is interpreted to support risk management decisions (e.g., recommended mitigation strategies) for humans and the affected environment.

3.2.1 HAZARD ASSESSMENT

Severity with respect to human health is determined using toxicological and/or epidemiological data that are used to determine how much of an insecticide a person may be exposed to without suffering significant adverse effects. With the exception of microbial larvicides, insecticides as a class function as neurotoxicants—their efficacy as well as many of their toxic effects in humans relate to their effects on the nervous system. For example, organophosphate pesticides inhibit the action of the nervous system enzyme acetylcholinesterase, and pyrethroid ester insecticides affect the flow of ions across the neuronal cell membrane. The focus of this hazard assessment was on the identification of human health benchmarks that can be used to quantify noncancer hazard (especially for neurological endpoints) and cancer risk for exposure

routes and durations relevant to workers/operators and residents that are likely to come in contact with insecticides through different interventions.

Consistent with recommendations in USEPA, 2005, and USEPA's Registration Eligibility Documents (REDs), health benchmarks were selected for three types of exposures

1. Acute exposures between 1 and 30 days
2. Intermediate or subchronic exposures from 30 days to 6 months, and
3. Chronic exposures greater than 6 months.

The data sources considered in selecting appropriate health benchmarks are generally consistent with recommendations from the USEPA and the WHO. Annex E provides specific citations for each of the benchmarks; however, the most important sources of information for health benchmarks (and toxicity information, generally) included

- USEPA's Reregistration Eligibility Decision (RED) documents, or risk assessments documented in the Federal Register supporting same
- USEPA's Integrated Risk Information System (IRIS)
- USEPA's Health Effects Assessment Summary Tables (HEAST) (USEPA, 1997b)
- Agency for Toxic Substance and Disease Registry's Toxicological Profiles
- Material Safety Data Sheets (MSDS)
- International Centre for Pesticide Safety
- Hazardous Substances Data Base, and
- Toxnet/PubChem/Published literature.

For chronic exposures, two types of health benchmarks were identified as part of the hazard assessment.

1. For noncancer hazard, the health benchmark is called the reference dose (RfD). The RfD represents a point (in milligrams of ai per kilogram body weight per day) on the dose–response continuum below which adverse effects would not be anticipated. That is, a dose below the RfD would not be expected to cause an adverse health effect. The RfD is defined by USEPA as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (USEPA, 1989). It can be derived from study data that report a no observed adverse effect level (NOAEL), a lowest observed adverse effect level (LOAEL), or a benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. The degree of uncertainty and confidence levels in RfDs vary and are based on both scientific (i.e., toxicological studies) and policy (i.e., level of conservatism) considerations. Noncarcinogenic effects are generally assumed to manifest only when exposure exceeds a threshold and not when exposure is less than the threshold or at some time following the exposure.
2. For cancer risk, the cancer slope factor (CSF) represents a plausible upper-bound estimate of the lifetime probability of developing cancer associated with exposure to a specific quantity of a potential carcinogen (USEPA, 1989). A CSF is expressed in units of risk per dose ([milligrams of pesticide per kilogram body weight per day]$^{-1}$). The CSF model of carcinogenicity is based on the assumption that *any* exposure is associated with some finite probability of an individual contracting cancer (i.e., no threshold for cancer). The CSF is commonly an upper-bound estimate (approximating a 95 percent confidence limit) of the increased human cancer risk from exposure to an agent over the lifetime of the individual (USEPA, 1989). Unlike RfDs, CSFs do not represent "safe" exposure levels; rather, they relate levels of exposure to a probability of developing cancer. Because there may be a decades-long latency period between exposure and effect (USEPA, 2005), carcinogenic effects are averaged over an entire lifetime.

As with previous risk assessments of insecticides conducted by USAID, a number of gaps related to the availability of health benchmarks for different exposure durations and exposure routes were identified. To fill

gaps for exposure duration, we used the longer-duration benchmark as a surrogate for the shorter-duration benchmark. For instance, a chronic health benchmark was often used as the subchronic benchmark when data on subchronic exposures were not identified. To fill gaps regarding exposure routes, we used route-to-route extrapolation as recommended in 2007 MVC PEA, under the simplifying assumption that there are no portal-of-entry effects and the route of administration is irrelevant to the dose delivered to the target organ. For example, we used the methodology published by USEPA for making route-to-route extrapolations for systemic effects via percutaneous absorption (USEPA 2004). In addition, we converted inhalation benchmarks in units of concentration to units of dose (mg/kg-day) based on an assumed inhalation rate of 20 m^3/day and an average adult body weight of 70 kg. [10]

The human health benchmarks for the insecticides included in this update are summarized in Annex D, Table D-3. In addition, the toxicological profiles presented in Annex E provide detailed information on each insecticide including, for example, health effects, toxicokinetics (e.g., information on absorption), typical uses, environmental behavior, and ecological effects on non-target organisms.

3.2.2 EXPOSURE ASSESSMENT

Whereas the Hazard Assessment is focused primarily on the development and selection of human health benchmarks, the exposure assessment is focused on developing the information needed to calculate the systemic daily dose. Included in the exposure assessment are concentration, contact rate, and body weight. Some of these terms are related specifically to the type of intervention (e.g., concentration), and other terms are related to the human receptors (e.g., body weight). The three major groups of input data required for the exposure assessment include:

Concentration parameters were derived from empirical data and are primarily a function of the physical characteristics associated with handling and application (e.g., formulation type) rather than the chemical properties of individual active ingredients (see USEPA 2015). Examples of concentration parameters and corresponding values include:

Table 3-1. Examples of concentration parameters

PARAMETER	DESCRIPTION AND UNITS	VALUE*
UE_{inhal}	mg ai inhaled per kg ai handled during spraying	0.066
UE_{derm}	mg ai deposited on skin per kg ai handled during preparation (open mixing of an emulsifiable concentrate)	0.49

1. USEPA 2015

In addition to direct exposures, we also evaluated indirect exposures through groundwater use (e.g., ingestion, dermal) following an application of larvicides. The exposure scenario for larvicide application involves treatment of "few, fixed, and findable" breeding areas with larvicides, often including shallow or even transitory waters typical of breeding habitats. Thus, the scenario does not consider "container breeding", and instead, is focused on targeted treatment of a few typical breeding habitats in a given area. Because the treatments likely involve shallow waters with potential drift to nearby soils, we used a simple transport model published by USEPA's Office of Pesticide Programs (OPP) called SCI-GROW (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment#scigrow) to account for adsorption, dilution, and attenuation (e.g., degradation) in the groundwater. This avoids unnecessarily conservative assumptions regarding the direct and immediate use of treated waters by residents, a practice that would be highly unlikely given WHO and USAID management of larviciding activities. As described by the USEPA, SCI-GROW is a very simple screening model that is used to estimate pesticide concentrations in vulnerable groundwater. The resulting concentrations are based on

[10] Note that all of these extrapolation techniques (e.g., route-to-route extrapolation) tend to be conservative and are only appropriate for screening purposes when discussed as part of the risk characterization.

environmental fate properties of the pesticide (aerobic soil degradation half-life and linear adsorption coefficient normalized for soil organic carbon content), the maximum application rate, and existing data from small-scale prospective ground-water monitoring studies at sites with sandy soils and shallow ground water. This simple model requires only four inputs: application rate, number of annual applications, organic carbon partition coefficient (K_{oc}), and soil half-life. The output groundwater concentrations are linearly related to both the application rate and number of annual applications. Rather than using default Dilution Attenuation Factors (DAFs), we selected this simple model because it is based on field observations and is applicable to vulnerable groundwater (e.g., shallow aquifers). Naturally, the screening model provides a relatively rough estimate of the groundwater concentration; however, the estimates of groundwater concentrations are reasonably conservative and, importantly, the model provides a much more reasonable representation of actual exposures when compared to direct use of larvicide-treated waters (i.e., sticking a straw into a recently treated waterbody).

Pesticide use parameters (e.g., application rates) generally describe how pesticides are applied and are typically taken from descriptions of field personnel regarding the use of insecticides for malaria vector management practices, as well as from manufacturer's recommendations. In addition, default values from the WHO are used when data are unavailable or considered of low quality. Examples of pesticide use parameters and corresponding values include:

Table 3-2. Examples of pesticide use parameters

PARAMETER	DESCRIPTION AND UNITS	VALUE
SR	Spray rate for IRS in houses/day	11
TCwall	Target concentration on walls in mg ai/m^2	specific to insecticide
SAwall	Surface area of treated walls in m^2/house	35.8

Receptor exposure parameters represent the characteristics of the receptor populations evaluated. These include adult, child, toddler, and infant residents of areas in Africa where the majority of malaria vector control interventions are implemented, and workers are engaged in malaria vector control activities. Examples of exposure factors and corresponding values include:

Table 3-3. Examples of exposure parameters

PARAMETER	DESCRIPTION AND UNITS	VALUE
$BW_{toddler}$	Body weight of toddler in kg	14
TE_{h2m}	Transfer efficiency from hand-to-mouth for toddler sleeping under LLIN (unitless)	0.1
BR_{sleep}	Breathing rate for adult while sleeping in m^3/hr	0.4

For each type of intervention, the exposure assessment is designed to estimate the concentrations to which workers/operators and residents may be exposed given the conditions described by the exposure scenario. Exposure scenarios are defined in terms of

- Receptor type (i.e., worker or resident)
- Activity (e.g., sleeping under a treated net; contact during spraying)
- Pesticide form (e.g., residual in treated material; wettable powder)
- Exposure route (e.g., dermal, inhalation, oral, breast milk)
- Age cohort (i.e., adult, child, toddler, infant)
- Exposure (acute, subchronic, chronic)
- Safety measure (i.e., consistent with guidelines, or lax personal protection)

The exposure scenarios for workers/operators primarily include mixing/loading and treating/application of the insecticide for dermal and inhalation pathways for adults. The exposure scenarios for residents primarily

include post-application and direct contact pathways with insecticide-containing materials for adults, children, toddlers, and infants. **Figures 3-1** and **3-2** illustrate the scope of the exposure assessment across interventions and receptors for workers and residents, respectively.

Detailed descriptions of each exposure scenario by intervention are included in Annex F, Tables F1-1 through F1-4.

Figure 3-1. Exposure Scenarios for Workers

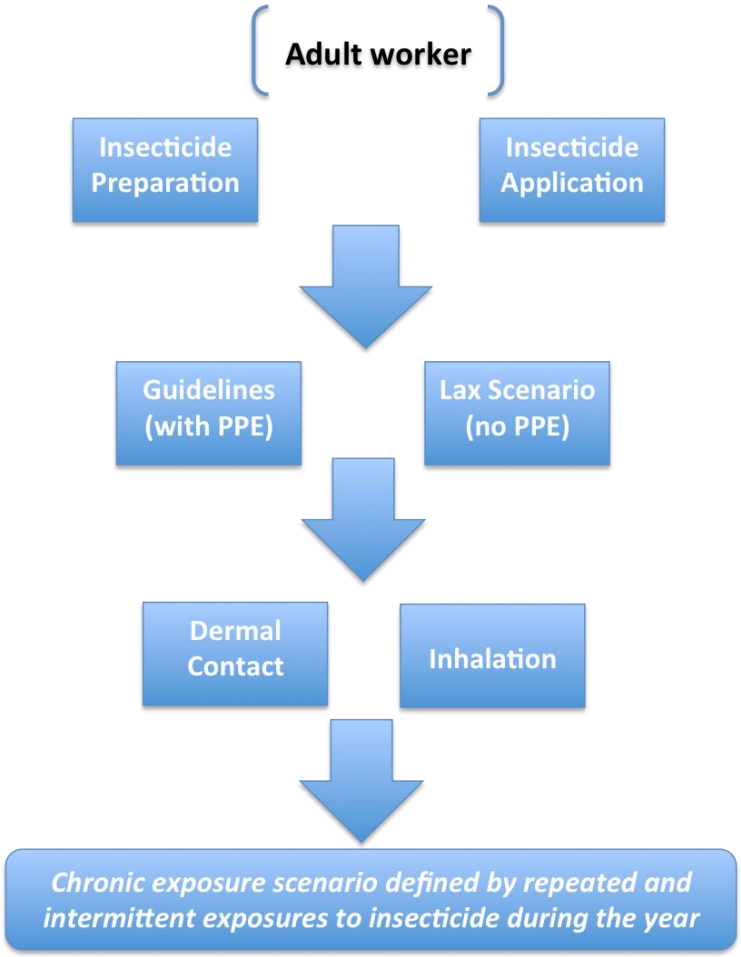
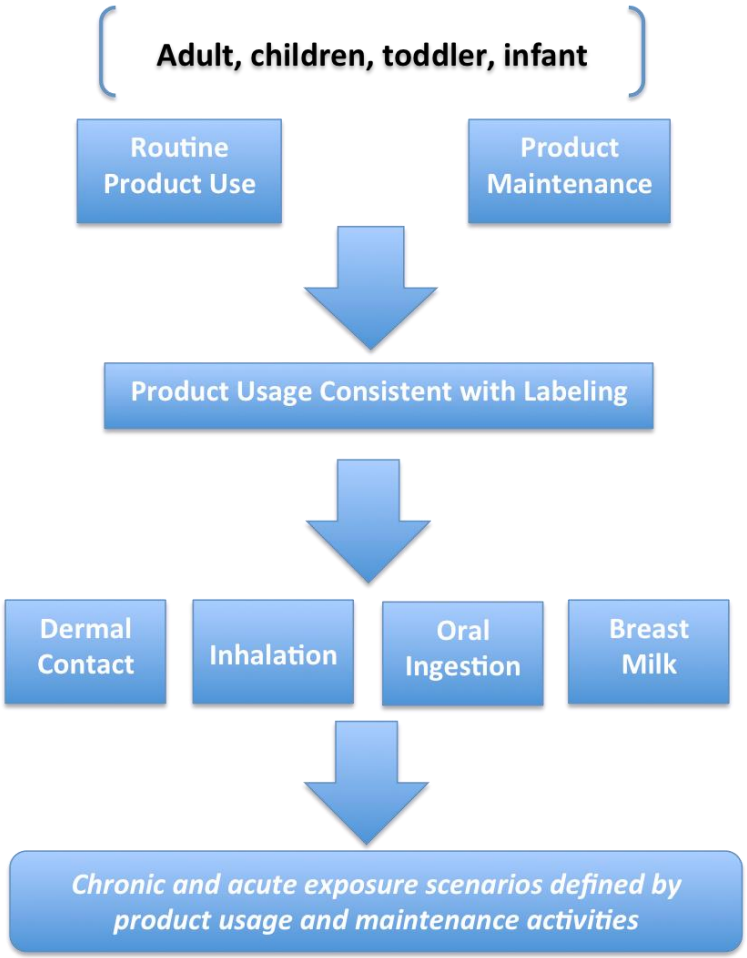


Figure 3-2. Exposure Scenarios for Residents



3.2.3 HUMAN HEALTH RISK CHARACTERIZATION

The risk characterization combines all of the information from the Hazard and Exposure Assessments to generate quantitative estimates of the potential health risks to workers and residents for the exposure scenarios identified under each intervention. The basic equations presented at the start of Section 3.2 are used to calculate the average daily systemic dose for acute, subchronic, and chronic exposures, as appropriate, and for each exposure scenario. As part of the Risk Characterization, the systemic dose for chronic and subchronic exposures is adjusted based on information describing the temporal characteristics of exposure, including

- ***Exposure Duration*** – the number of years that the exposure can occur based on the scenario description
- ***Exposure Frequency*** – the number of times, per year, that exposure is assumed to occur
- ***Averaging Time*** – the number of days over which the exposure is averaged

Taken together, these inputs are combined into an "Exposure Factor"[11] that represents the nature of the exposure (e.g., intermittent, chronic, lifetime) in a clear and consistent manner. The Exposure Factor is given by

$$Exposure\ Factor = \frac{Exposure\ Duration\ (yr) \times Exposure\ Frequency\ \left(\frac{days}{yr}\right)}{Averaging\ Time\ (days)}$$

For example, for an IRS worker that sprays an insecticide 72 days each year, the Exposure Factor for a chronic exposure scenario would be calculated as

$$Exposure\ Factor = \frac{1\ yr \times 72\ days/yr}{365\ days} = 0.197$$

where the Exposure Factor is used to adjust the average daily systemic dose for the intermittent exposure that occurs during the course of a year.[12] The Exposure Factor adjustment avoids an implicit assumption that exposure occurs every day, and adjusts the dose downward to account for the fact that the exposure is intermittent. For acute exposures, the Exposure Factor is irrelevant because the calculation simply produces the acute systemic dose for a day (versus an average daily dose), and compares that dose to an acute health benchmark. The risk calculation equations for each intervention and exposure scenario are presented in Annex F2, and a complete list of input parameter values for these equations is provided in Annex F3.

The quantitative risk results produced during the Risk Characterization include a series of risk outputs that correspond to the exposure scenarios identified as relevant to each intervention.

For noncancer effects, HQs are produced for acute, subchronic, and chronic exposures, as appropriate, for each scenario as defined under the exposure assessment. In addition, HQs are summed for aggregate exposures, including the

- total exposure across multiple routes (e.g., dermal + inhalation), and
- total exposure across scenario type by receptor type (e.g., worker mixing + spraying).

11 See https://www.atsdr.cdc.gov/hac/phamanual/appg.html

12 Note that if we assumed that the worker's "career" lasted for 5 years, the Exposure Duration would be 5 years, and the Averaging Time would be calculated as 5 years x 365 days/year, producing the same Exposure Factor value of 0.197.

For products that contain multiple active ingredients, the HQs are summed together for each of the above metrics, producing a conservative estimate of the noncancer hazard for the product. This additive approach is also used for products that contain piperonyl butoxide (PBO), a widely-used insecticide synergist that acts by protecting the co-applied insecticide (e.g., pyrethrins, pyrethroids) from metabolic attack by inhibiting an enzyme system that catalyzes oxidative processes in living systems. For active ingredients that have synergistic effects (i.e., toxicity is multiplicative rather than additive), the product HQ can be increased by some factor to account for the synergism. However, quantitative studies on active ingredient synergy are somewhat rare, and the determination of synergism is typically made on the basis of mechanism of action, and handled qualitatively in the Risk Characterization.

For cancer endpoints, the average daily systemic dose over the course of a lifetime (often referred to as simply the Lifetime Average Daily Dose, or LADD) is calculated over the assumed lifetime of the individual. The LADD is calculated by setting the Averaging Time to the individual's lifetime (50 years), with the Exposure Duration and Exposure Frequency corresponding to the exposure scenario. Using the same example for the IRS worker, the Exposure Factor would be calculated as follows

$$Exposure\ Factor = \frac{1\ yr \times 72\ days/yr}{18{,}250\ days} = 0.00394$$

Because cancer risk is expressed as a probability averaged over a lifetime, the LADDs for each age cohort are added together to calculate a total LADD.

For cancer endpoints, the ILCRs are produced for carcinogenic insecticides, regardless of the exposure type (e.g., acute, subchronic, or chronic) because, for most chemicals, cancer risk is widely believed to be a non-threshold event. That is, exposure at any time to even a small amount of a carcinogen carries some finite risk of cancer. The metrics for lifetime cancer risk are identical to those calculated for noncancer hazard, except that lifetime cancer risk is reported for the individual, rather than by age cohort.

The highest noncancer HQs and cancer ILCRs developed in the Risk Characterization are summarized by intervention and product/active ingredient in Section 4, which also contains a narrative that explains the conclusions and recommendations. The narrative considers the hazard profile of each new product/active ingredient with respect to other insecticides used in the intervention, and as appropriate, discusses available qualitative and semi-quantitative information that provides additional insight into the model results. The conclusions also include recommendations regarding the use, management, and end-of-life treatment of products that may contain insecticide residuals.

The detailed results for each exposure scenario are presented in Annex C.

3.3 ENVIRONMENTAL RISK ASSESSMENT

22 CFR 216 requires that environmental assessments describe the affected environment in detail and identify any potential adverse effects on that environment. Additionally, it requires that environmental assessments of pesticide use describe the "conditions under which the pesticide is used, including climate, flora, fauna, geography, hydrology, and soils." This PEA is broad by design, and should not be used to characterize ecological effects for the diverse environments where USAID will support malaria control interventions. The characterization of potential risks to human health is focused on effects to individuals; in contrast, the characterization of potential risks to the environment should be performed at a higher level of biological organization (e.g., population, community), and requires the identification of specific ecosystem attributes that are considered worth protecting because of their social or economic value. The evaluation of these attributes should, at some level, seek to balance the potential loss in ecological structure/function against the benefits to public health as part of the malaria vector control program. Moreover, because ecological systems

are complex, include numerous redundancies, and are capable of recovery, characterizing "adverse effects" should reflect the specific context and environmental conditions within which the insecticide is used.

Supplemental Environmental Assessments and other required approval documents are the second tier of the environmental assessment process, and are conducted to address the affected environment on a country-by-country basis. Guidance on writing the Affected Environment section of SEAs and other required approval documents is provided in the SEA Guidelines in Annex J. To summarize, the following requirements have been identified for the SEA:

- Malaria incidence and prevalence in the country and identification of endemic and epidemic-prone areas
- Population in targeted area
- Administrative boundaries
- Socioeconomic data
- Land area targeted
- Ecological zones
- Climate of affected/targeted area
- Flora and fauna in affected/targeted area, with specific concern for:
    - Endangered species that could be harmed by pesticide exposure
    - Protected areas, forest and water resources where spraying of pesticides should not take place, and where buffer zones may be warranted
    - Land use patterns
- Geography of affected/targeted area
- Hydrology of affected/targeted area, and
- Soils of affected/targeted area.

As part of the harmonization of risk assessment methods, USAID recognized that the safety recommendations and BMPs (described in Section 2.0) provide significant protection from adverse ecological impacts for exposure scenarios associated with most interventions, including IRS, LLINS, insecticide-treated clothing, and LLIHS. Not surprisingly, the WHO GRAMs for IRS and ITNs do not include recommendations for the assessment of ecological risk.

However, the WHO GRAM for larviciding presents a basic framework for ecological risk assessment, noting that risks associated with the direct application of larvicides into the aquatic environment should be evaluated for non-target organisms, including nearby terrestrial ecosystems when appropriate.

Therefore, the ecological risk assessment methodology described below is focused exclusively on larvicides as the intervention option that has the greatest potential for adverse ecological effects. The methodology is consistent with the GRAM and best practices in ecological risk assessment, and develops meaningful insights into the potential risks associated with different larvicide formulations included in the PEA. The semi-quantitative methodology is organized around the risk assessment paradigm described in Section 3.1 for human health—hazard assessment, exposure assessment, and risk characterization. In the future, should USAID determine that other interventions, management practices, or end-of-life issues require further evaluation for ecological impacts, this methodology will be updated to address those needs.

3.3.1 HAZARD ASSESSMENT

Larvicides are specifically developed to kill invertebrate organisms during developmental stages (e.g., eggs, larvae, pupae), and therefore, toxicity to other arthropods with similar life cycles can be expected. However, for other non-target organisms, the assessment of hazard is central to characterize potential ecological risks. Severity with respect to adverse effects on non-target organisms should address endpoints that are relevant to population dynamics and/or community structure and function.

For species populations (e.g., fish), these endpoints may be evaluated during acute and chronic exposure studies, particularly during development stages, and can be grouped into several major categories:

- Mortality/lethality
- Growth and survival
- Reproductive fitness

For communities (e.g., sediment, soil community), these endpoints also include measures of:

- Abundance/diversity
- Species composition/richness
- Function (e.g., nitrogen fixation)

Actual effect levels are preferred for these endpoints when available. For example, an Effective Concentration for 20% of the population (an EC_{20}) is preferred to a No Observed Effect Concentration (NOEC) because (1) we lack the ability to distinguish less than a 20% variation in natural, healthy populations and (2) the NOEC represents a point estimate of the concentration at which the effect under study was not observed, a measure that has limited ecological relevance within the broader context of the ecosystem.

Larviciding activities can potentially affect both aquatic and terrestrial ecosystems, and in rare cases, larvicides may bioaccumulate in the food chain. Therefore, toxicity data should be selected to represent different taxa (e.g., invertebrate versus vertebrate), trophic levels, routes of exposure (e.g., ingestion versus direct contact), and levels of biological organization (e.g., population versus community).

For ***aquatic ecosystems***, toxicity data for non-target organisms should include

- Microalgae (e.g., green algae)
- Aquatic invertebrates (e.g., daphnids)
- Aquatic vertebrates (e.g., fish)

For ***terrestrial ecosystems***, toxicity data for non-target organisms should include

- Soil microbiota (e.g., nitrogen-fixing bacteria)
- Terrestrial invertebrates (e.g., earthworms, bees)
- Terrestrial vertebrates (e.g., mammals, birds)

The primary data sources used in compiling toxicological data for the hazard assessment include

- U.S. Environmental Protection Agency (USEPA) sources such as the OPP Pesticide Ecotoxicity Database (http://www.ipmcenters.org/ecotox/)
- Published reports from international agencies such as the WHO on pesticide use and toxicity
- Data published by US organizations such as the National Oceanic and Atmospheric Administration or the Los Alamos National Laboratory ECORISK Database
- Compendia of peer-reviewed values such as EXTOXNET, PAN, or the Hazardous Substance Database
- Peer-reviewed literature and published "grey" literature

There are two types of ecological benchmarks that are identified in these sources. First, to evaluate potential ingestion exposure for animals, effects levels are typically given in the same units as dose for human health risk assessment (mg ai/kg-day). Second, for other exposure routes (e.g., direct contact) and for community-level effects, effects levels are typically given in units of concentration (e.g., mg ai/kg soil, mg ai/L water).

3.3.2 EXPOSURE ASSESSMENT

The potential for exposure to larvicides for non-target organisms is a function of the application method, the environmental behavior of the larvicide once released, and the environmental characteristics of the waterbody and catchment area. The latter cannot be adequately evaluated for the PEA; therefore, the focus of the

exposure assessment is on (1) the potential for migration of the larvicide from the waterbody to the nearby terrestrial habitats, and (2) the magnitude and duration of potential exposure to non-target organisms.[13]

Migration to Terrestrial Ecosystems—Larviciding activities can affect terrestrial ecosystems as well as aquatic ecosystems depending on the application method used. For larvicides that require "low energy" for application (e.g., tablets, dispersed granules), the exposure assessment will focus exclusively on the aquatic ecosystem. However, for "high energy" application such as the aerial spraying of larvicides, or for larvicides that are particularly volatile, dispersion can result in larvicide contamination of nearby terrestrial ecosystems.

Following application, the mobility of the larvicide is a function of properties such as sorption to organic matter in the surface water and sediment. The partitioning among different environmental compartments will determine movement in the environment, with more mobile compounds potentially migrating to terrestrial ecosystems. Environmental mobility[14] can be predicted to some degree using certain chemical-physical properties such as:

- Henry's Law Constant
- Vapor Pressure
- Solubility
- Partition coefficients
  - Octanol-Water (K_{ow})
  - Org. Carbon-Water (K_{oc})
  - Soil/Sediment-Water (K_d)

Magnitude and Duration of Exposure—The potential for exposure to a larvicide can be determined on the basis of specific chemical and physical properties that are routinely used to assess persistence and bioaccumulation potential; the more persistent the larvicide, the more likely an exposure will occur through direct contact, and the more bioaccumulative the larvicide, the more exposure can occur through the food chain. During the exposure assessment, an environmental exposure profile can be developed based on published information as well as chemical-physical properties related to environmental persistence and bioaccumulation, as shown in Table 3-4.

Table 3-4. Components of an Environmental Behavior Profile

PERSISTENCE	BIOACCUMULATION
▪ Half-life water ▪ Half-life soil ▪ Rate constants, e.g., ➢ Biodegradation ➢ Photolysis ➢ Hydrolysis	▪ Bioconcentration factors ▪ Bioaccumulation factors ▪ Partition Coefficient (K_{ow})

3.3.3 ECOLOGICAL RISK CHARACTERIZATION

There are two main objectives for the ecological risk characterization. First, in absolute terms, the risk characterization should determine whether the potential risks to the affected environment are such that the larvicide should not be approved for use. Circumstances that would make this finding likely would be the use of a larvicide that is highly toxic to species across multiple taxa and trophic levels (i.e., the **severity** of effect to the ecosystem is considered high), and is highly persistent in the environment (i.e., the **probability** of

13 USAID recognizes that larvicides are also applied to standing water that, while serving as a mosquito breeding ground, is not sufficient to sustain a recognizable aquatic ecosystem.

14 These mobility measures are not independent; algorithms are generally used to estimate Henry's Law Constant from solubility and vapor pressure.

exposure is considered high). For larvicides with these attributes, even well-designed mitigation strategies may not be sufficient to reduce risk to acceptable levels because larvicides are directly applied to the environment. However, larvicides are typically designed to degrade quickly in the environment (e.g., hydrolysis, photolysis), are low to moderately mobile in the environment, tend to bioaccumulate weakly in the food chain, and exhibit the highest toxicity to developmental stages of aquatic invertebrates, with variable toxicity to other non-target organisms.

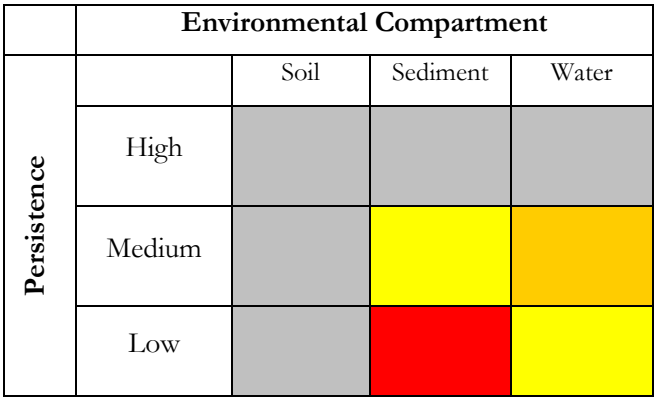
The second objective for the ecological risk characterization is to provide *relative* information on risk to the affected environment for aquatic ecosystems, and when appropriate for terrestrial ecosystems. Recalling that USAID is concerned with the risk to ecological values (e.g., impact on local fish farms) rather the risk to an individual organism, and that the choice of a larvicidal agent depends on the specific country-level vector control strategy, the ecological risk characterization for the PEA needs to provide a scheme with which to compare larvicides. There are different approaches to characterize relative risks to support decision making, from quantitative risk ranking, to semi-quantitative risk mapping, to qualitative narratives (i.e., the weight-of-evidence approach). To some degree, these approaches share the same underlying concept, namely, they integrate information on persistence, bioaccumulation, and toxicity. For the HAARP presented in this PEA update, USAID has developed a hybrid approach that maps available data in a semi-quantitative scheme, creating an exposure profile (based on indicators of environmental behavior) and a toxicity profile (based on available toxicity data) for each larvicide. In essence, maintaining separate profiles ensures that risk managers can consider the *severity* of potential effects and the *probability* of exposure, and avoid misinterpreting risk results by calculating a "risk index" from ordinal values.

The hybrid approach is consistent with recommendations in the larvicide GRAM, reflects best practices in semi-quantitative risk characterization, and provides meaningful information for decision-making purposes. The approach involves four basic steps:

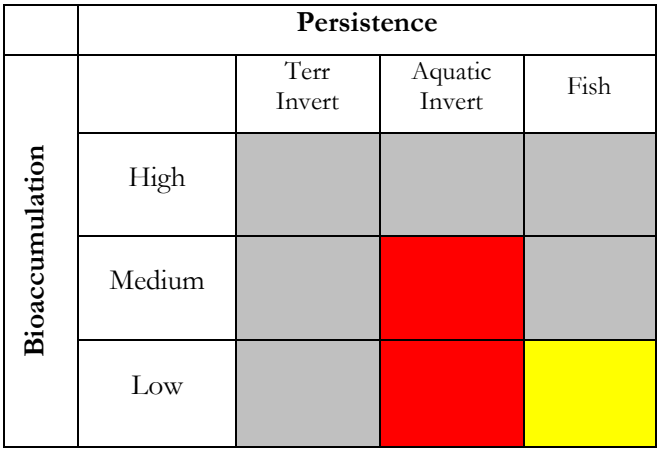
1. Identify the list of input variables that can be used to score persistence, bioaccumulation, and toxicity.
2. Establish "bins" for high, medium, and low for each input variable for persistence and bioaccumulation.
3. Establish "bins" for high, medium, and low for toxicity for each of trophic category.
4. Score each of the input variables according to the bins, and create the heat map by using "hotter" colors to indicate number of entries in each bin.

As suggested in the hypothetical example in **Figure 3-3**, heat maps provide a picture of the data availability (i.e., lack of warm colors means that there are significant data gaps), the variability in the data (i.e., reading down the high, medium, low categories, warm colors in multiple cells show that the data are highly variable), and indicate the level of information available supporting a high, medium, or low qualitative rating. The use of heat maps to visualize ecological risk has several advantages over approaches that use persistence, bioaccumulation, and toxicity information to rank or, in some way, collapse different types of information into a single index. First, there are no minimum data requirements; the heat map is developed using available information on suitable input variables, and can be appended as new information becomes available. Thus, the map provides information on the availability of data as well as the range of the input parameter values. Second, the information can be semi-quantitative (e.g., LC_{50} below 1 mg/L is considered "low" for a daphnid test) and/or qualitative (e.g., "studies report that spinosad cannot be detected 48 hours after application). Third, the maps provide complementary information to the narrative, and represent information on adverse ecological effects in a manner that is consistent with the level of certainty in using laboratory data on study species to infer potential adverse effects to valued ecosystems.

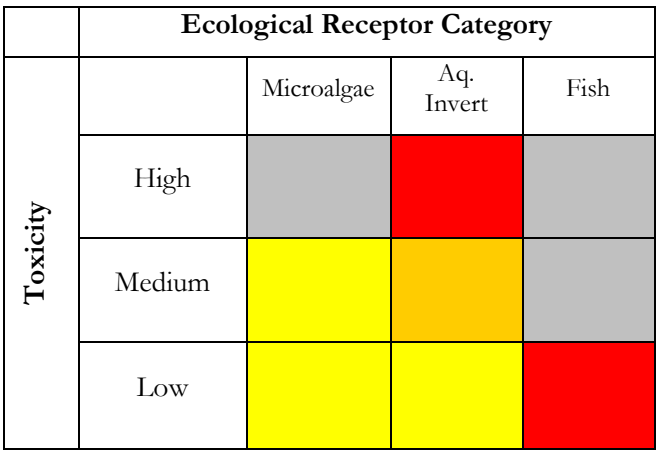
Figure 3-3. Hypothetical Risk Characterization



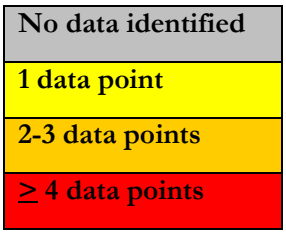
The persistence heat map is limited to the aquatic ecosystem given the granule application to surface water. The data indicate that the larvicide is low to moderately persistent in the sediment and water compartments. The majority of the data suggest that persistence in sediment is low.



The bioaccumulation heat map indicates that the larvicide can be taken up by aquatic invertebrates and fish, low to moderate. Fish that consume invertebrates could be exposed via the food chain. Because the application is via granules, no data were included for the terrestrial ecosystem.



This toxicity heat map includes only aquatic receptors only for illustrative purposes. The map suggests low-medium toxicity to microalgae, high toxicity to invertebrates, and low toxicity to fish.



4.0 SUMMARY OF RISK RESULTS

In this section, we present a summary of the human health risk results for insecticides proposed for each of the five interventions—including new products, combinations of active ingredients and synergists, and repurposed insecticides—along with a narrative description of the potential for adverse ecological effects for larvicides. As described in Section 3.1, the quantitative health risk characterization is based on the HQ for noncancer effects, and the ILCR for carcinogenicity. The threshold criterion for noncancer effects is an HQ = 1; HQ values below 1 strongly indicate that significant adverse effects are not expected, and HQ values above 1 indicate that adverse noncancer effects are possible. The quantitative screening of noncancer hazard is a binary outcome, and does not provide information on the probability that an adverse effect will occur. However, given the conservative assumptions employed in the exposure assessments, the HQ represents a value at the upper bound of the inferred distribution of chemical hazard for exposed individuals. For that reason, the interpretation of the noncancer screening results is critical in determining how the risk assessment results are used. Put simply, an HQ of 10 does not imply that adverse effects *will* occur, or that the hazard is ten times more likely than with an HQ of 1. Rather, an HQ of 10 implies that it is possible that they occur given the conservative manner in which the exposure scenario was constructed, and that further evaluation of the exposure assumptions is warranted.

For cancer risk, a threshold ILCR of 1 in 10,000 (1E-04) is used as the acceptable excess risk of an individual contracting cancer over a lifetime. ILCR values below 1E-04 indicate that the risk of cancer is relatively low even though it is non-zero. Unlike an HQ, the ILCR is expressed as a probability. This probability is based on the dose-response model of carcinogenicity and does not address the probability of an individual actually being exposed to an insecticide at a level that causes cancer. Therefore, an ILCR above 1E-04 should not be interpreted to mean that an individual is actually likely to experience this cancer risk; rather, this should be interpreted in much the same way we interpret a screening HQ greater than 1. Cancer risks greater than 1 in 10,000 suggest that it is possible risk of cancer may exceed the threshold, but consideration should be given to the conservative manner in which the exposure scenario was constructed.

The focus of the conclusions is two-fold. First, the results for each new product are compared to other products to provide information on the relative risk posed by different insecticide products. This comparison, as well as efficacy and insecticide resistance data, will help inform the selection of intervention options by providing information about potential human health (and ecological) risks. All things being equal, USAID strives to select intervention options that pose the least risk to human health and the environment, and the results mining will provide USAID with useful insights into the relative risk associated with different insecticides and formulations. Second, this section establishes the basis for active ingredients that are deemed acceptable by USAID for products under a specific intervention. For example, if an LLIN with a concentration of X mg/m^2 for permethrin and Y mg/m^2 for pyriproxyfen on material A is assessed, any LLIN with concentrations below X and Y mg/m^2 for permethrin and pyriproxyfen on material A would be considered already assessed from an environmental perspective under USAID's PEA. That is, the new product would not have to undergo a formal risk assessment. This will help promote the development and rapid deployment of safe and effective products for the malaria vector control program.

For each intervention, three critical pieces of information are presented. First, we present a **quick reference table** of the highest HQ or cancer risk values from any of the exposure scenarios. This single risk result is useful in that it determines whether or not there is *any* potential for adverse effects to workers or residents based on the exposure scenarios that were screened. Second, we present a summary figure that shows the **aggregate risk** results across exposure scenarios for worker and residential receptors, respectively. The figure provides relative risk information on each of the products. Also for each receptor, the figure shows whether the highest aggregate risk is below the target HQ of 1, in the HQ range suggesting *some* potential concern ($1 > HQ \leq 10$), or in the HQ range where the mitigation plan should specifically address actions to reduce exposure ($10 > HQ \leq 100$). No HQ values for any exposure scenarios were above a value of 100. Note that, when there is no bar corresponding to a receptor, this means that the HQ results were below 0.01. Cancer

risks are not shown graphically because only two chemicals (permethrin and 4-chlorophenyl urea, a water degradation product of diflubenzuron) were considered as possible human carcinogens. Third, we present the **risk profile** for each product that captures all of the HQ values calculated by the screening model. These charts are shown on a single page for workers and residents, respectively, and provide information on the relative importance of different exposure pathways—dermal, oral, and inhalation—that were considered in this risk assessment. Three HQ "bins" were selected to illustrate the risk profile: (1) for simplicity, we collapsed the two lowest HQ values shown on the x axis for the aggregate exposures into a single bin, HQ $\leq$ 1, (2) the second bin, 1 > HQ $\leq$ 10, indicates that there is *some* potential for adverse health effects, and (3) the third bin, HQ > 10, includes HQ results that warrant specific actions in the mitigation plan.

4.1 INDOOR RESIDUAL SPRAYING

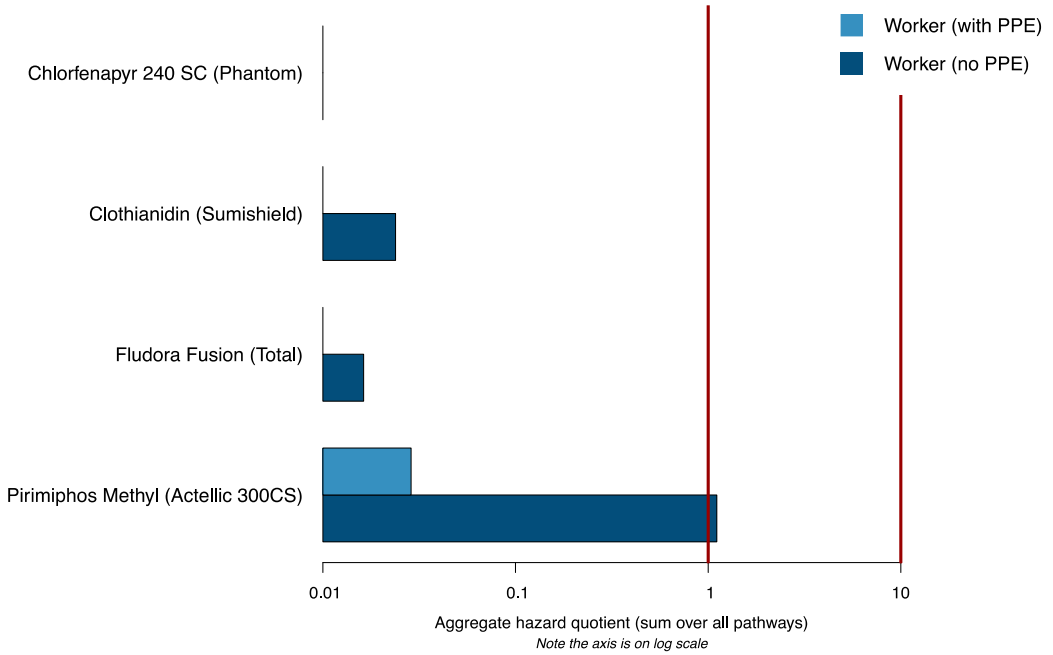
Table 4-1 presents the highest HQ results for total exposure across all receptors for each product; of the four new IRS products included in this update, only Actellic 300 (pirimiphos-methyl CS 300) exceeds the target HQ of 1.

Table 4-1. Highest Risk Results for IRS Products

ACTIVE INGREDIENT (PRODUCT)	HIGHEST RISK RESULT	EXPOSURE SCENARIO LEADING TO HIGHEST RISK RESULT
Clothianidin (Sumishield)	HQ = 0.90	**Noncancer hazard**: total exposure for the infant, including inhalation and breast milk (post application)
Clothianidin and deltamethrin (Fludora Fusion)	HQ = 0.63	**Noncancer hazard**: total exposure for the infant, including inhalation and breast milk (post application)
Chlorfenapyr 240 SC (Phantom)	HQ = 0.13	**Noncancer hazard**: total exposure for the toddler including dermal, inhalation, and hand-to-mouth (post application)
Pirimiphos-methyl CS (Actellic 300 CS)	HQ = 49	**Noncancer hazard**: total exposure for the toddler including dermal, inhalation, and hand-to-mouth (post application)

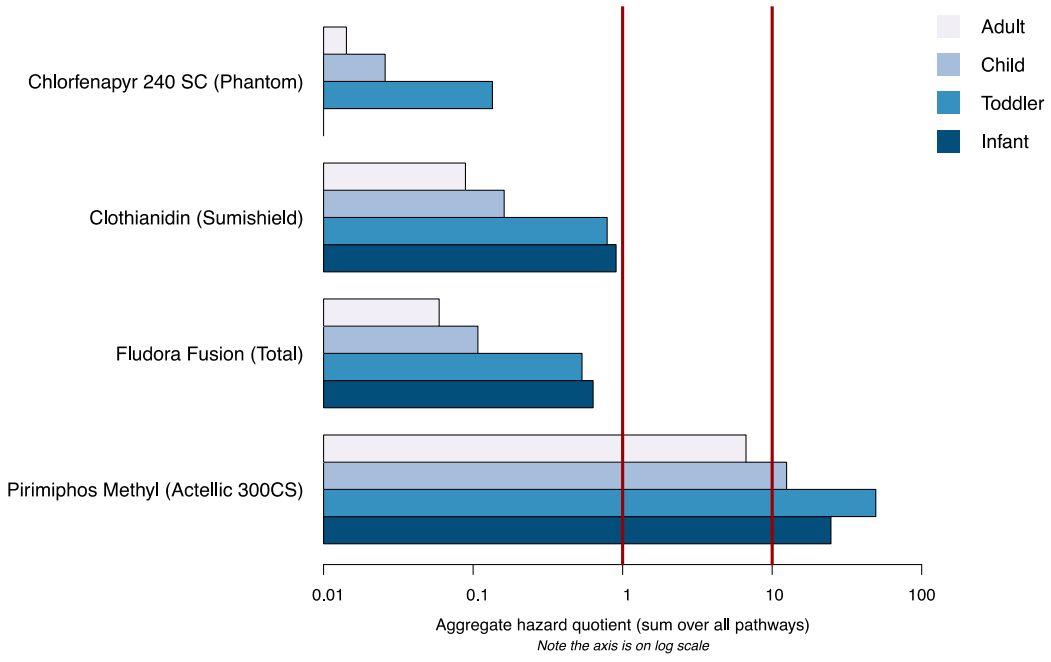
Figures 4-1 and **4-2** present the risk assessment results for the four IRS products aggregated across exposure scenarios for worker and resident receptors, respectively. For example, the worker exposure scenarios include the pesticide preparations as well as the spray application and cleanup. For workers, the results show that risks are extremely low for the "with PPE" scenarios (i.e., more than an order of magnitude below the target HQ of 1), and that the risks are also not at levels of concern for the "no PPE" scenarios. However, it will remain a best practice to enforce use of PPE for application of all insecticides.

Figure 4-1. Aggregate HQs – Chronic Exposure for Workers



For residential receptors, the results show that, for three of the four products, aggregate exposures are all below the target HQ of 1. The risk estimates for Actellic 300CS (pirimiphos-methyl CS) suggest that there is *some* potential for adverse health effects associated with this product, and that the mitigation plans will include mitigation measures to reduce post-application exposures to infants and toddlers.

Figure 4-2. Aggregate HQs – Chronic Exposure for Residents



4.1.1 HUMAN HEALTH RISK

In **Figures 4-3 and 4-4** the risk profiles for each of the products are visualized and the results are further discussed in this section. For workers and residents, respectively, these figures summarize all of the HQs calculated by the dermal, oral, and inhalation exposure routes. For example, IRS workers are exposed to insecticides via three pathways – dermal via mixing/loading, dermal via spraying, and inhalation via spraying. With PPE, all three pathways for Chlofenapyr 240 SC yielded HQs less than 1, hence there are three counts in the "less than 1" category.

Clothianidin (Sumishield)—The risk results for clothianidin are based on a two-generation reproduction study on rats in which the rats were exposed through normal feeding; endpoints included weight gain, sexual maturation, and stillbirths. The health benchmark derived from this study, and recommended by the USEPA (USEPA 2012), is 0.0098 mg/kg/day. This value was calculated using an Uncertainty Factor (UF) of 100 to account for differences in intraspecies sensitivity (10), and the lack of human exposure studies (10). In addition, a Modifying Factor (MF) of 10 was also applied to capture uncertainty associated with the lack of a developmental immunotoxicity study (a requirement under USEPA pesticide registration guidelines). The application of the same health benchmark across all exposure durations and exposure routes provides a conservative representation of toxicity as absorption is typically higher for oral administration than dermal contact, and the physiological response to shorter exposures allows for recovery (in contrast with chronic exposures). Based on the risk screening results and the inherently conservative nature of the calculation, adverse human health effects for workers or residents are not expected from the use of clothianidin.

Clothianidin and deltamethrin (Fludora Fusion)—The risk results for Fludora Fusion are based on the same study on clothianidin as that used for Sumishield and, for deltamethrin, an acute study on neurological effects in rats (used for oral and inhalation), and an acute dermal contact study on rats that observed local effects on the skin. The USEPA determined that there was no apparent increase in hazard with repeated or chronic exposures, so the benchmarks derived from the acute studies were used directly as benchmarks for intermediate and chronic exposures (USEPA 2004). All derived RfDs were based on a UF of 100 that represented differences in intraspecies sensitivity (10), and the lack of human exposure studies (10). Based on the risk screening results, adverse health effects for workers or residents are not expected.

Chlorfenapyr SC 240 (Phantom)—Worker risk associated with mixing/loading and spraying chlorfenapyr SC 240 were orders of magnitude below levels of concern (e.g., the HQ for total worker risk for lax scenarios with no PPE was 0.0044). Similarly, resident risks were also below an HQ of 1, with the highest risk associated with total exposure for the toddler, including dermal contact, inhalation, and hand-to-mouth behavior. The toxicological data set developed for chlorfenapyr includes oral and dermal studies; for inhalation, an oral study was used to derive a health benchmark of 0.026 for chronic exposures, assuming that 100% of any inhaled dose was readily available, and that there were no portal of entry effects. The latter assumption is well-supported in the occupational exposure literature. Based on the results of health risk screening, use of this product under the IRS intervention provides a safe and effective option for malaria vector control.

Pirimiphos-methyl CS—Worker risk associated with spraying pirimiphos-methyl is slightly above the target HQ of 1 for the lax scenarios (1.1). The HQs calculated for the guidelines scenarios are below 0.029, suggesting that the potential for adverse effects to workers would be mitigated even with partial compliance to basic safety practices. For all resident receptors (i.e., adult, child, toddler, and infant), the screening results are above the target HQ of 1, with HQs of 6.7, 12, 49, and 25, respectively. The human health benchmarks for pirimiphos-methyl are derived, primarily, from a single study on neurological effects in rats in which a NOAEL was not identified; consequently, the health benchmarks all include an additional safety factor of 10 to address the uncertainty in benchmark derivation using a LOAEL rather than a NOAEL. Uncertainty factors of 300 (dermal and inhalation routes) and 1,000 (oral route) were applied by USEPA, reflecting the high level of uncertainty in the available data. The USEPA's Interim Reregistration Eligibility Decision (RRED) in 2001 was the source of the health benchmarks, indicating the need for a more complete toxicological analysis of pirimiphos-methyl. Despite the paucity of quality toxicological data for different

exposure routes and durations, the results are suggestive of the *potential* for adverse effects because (1) all residential receptors are above levels of concern, and (2) neurological effects are considered serious in terms of risk management. The driving exposure routes for toddlers are dermal contact and inhalation, and for infants the driving exposure route is inhalation. Both toddlers and infants have more rapid inhalation rates (relative to body weight) than adults, and are therefore more susceptible to adverse health effects via this exposure route.

4.1.2 CONCLUSIONS

As previously stated, based on the risk screening results and the inherently conservative nature of the calculations, adverse human health effects for workers or residents are not expected for from the use of Clothianidin, Clothianidin/Deltamethrin, or Chlorfenapyr in IRS. The potential for noncancer effects indicated by the risk screening for Actellic 300CS suggests that additional precautions should be explored by USAID, particularly infants and toddlers, to decrease dermal exposure following spraying. In the next year, PMI will support an operational research study with Actellic 300CS to determine if spraying only the top half of a wall surface is as effective as spraying the whole surface of the wall; results of the operational research study will be used, in part, to refine standing operating procedures, and if spraying the top half only is deemed effective, then this practice will negate toddlers' dermal exposure pathway. In addition, the limited toxicological data with which to derive health benchmarks could be addressed through the conduct of animal studies, specifically, to better understand the absorption and toxicology of dermal exposures to this product.

Figure 4-3. Risk Profile for IRS Workers (with PPE)

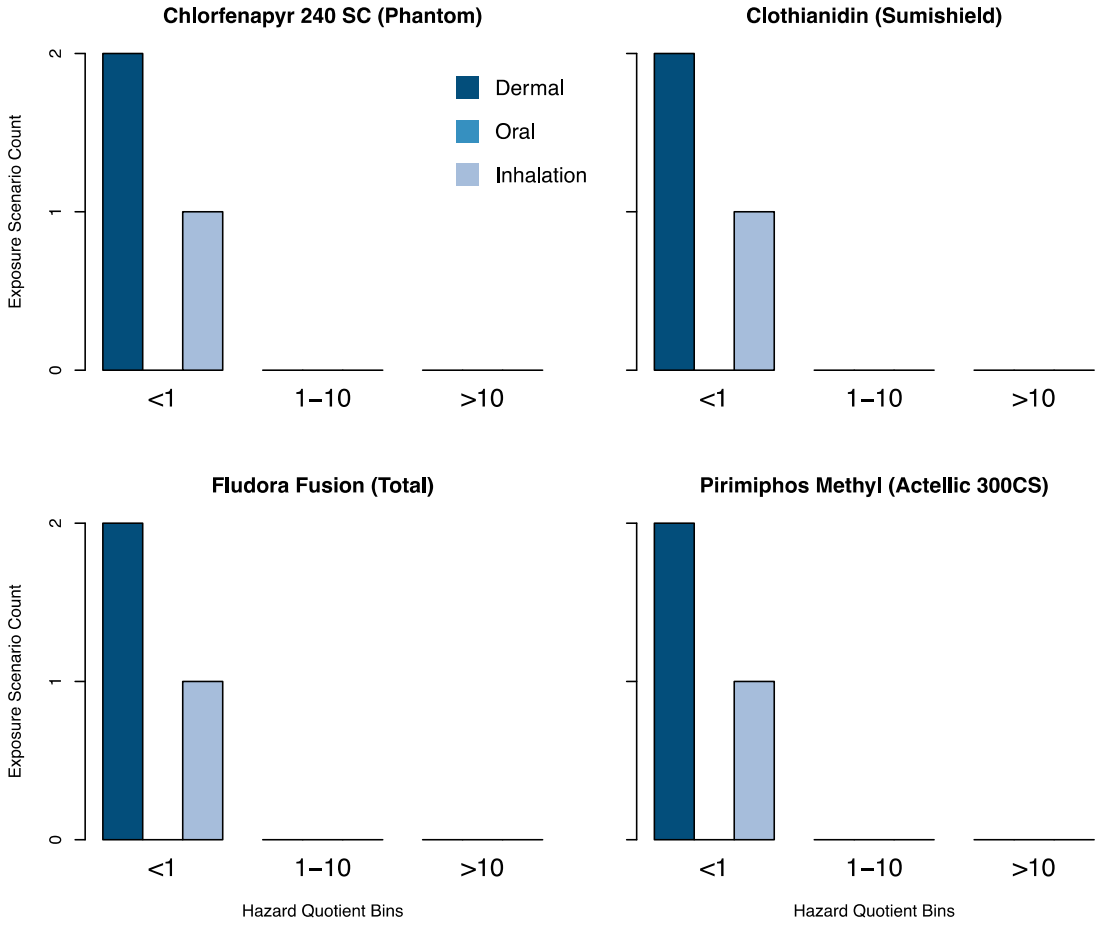
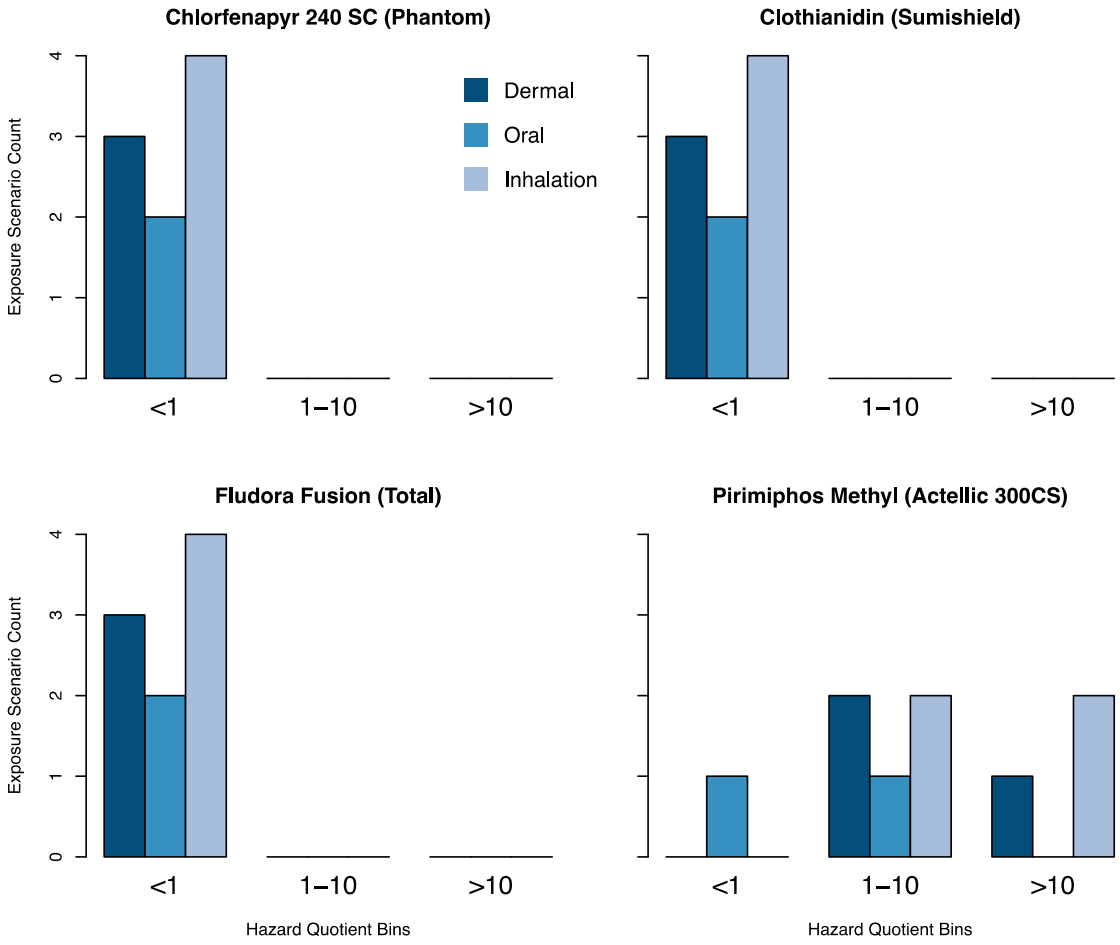


Figure 4-4. Risk Profile for Residents – Post Application



4.2 LONG-LASTING INSECTICIDAL NETS

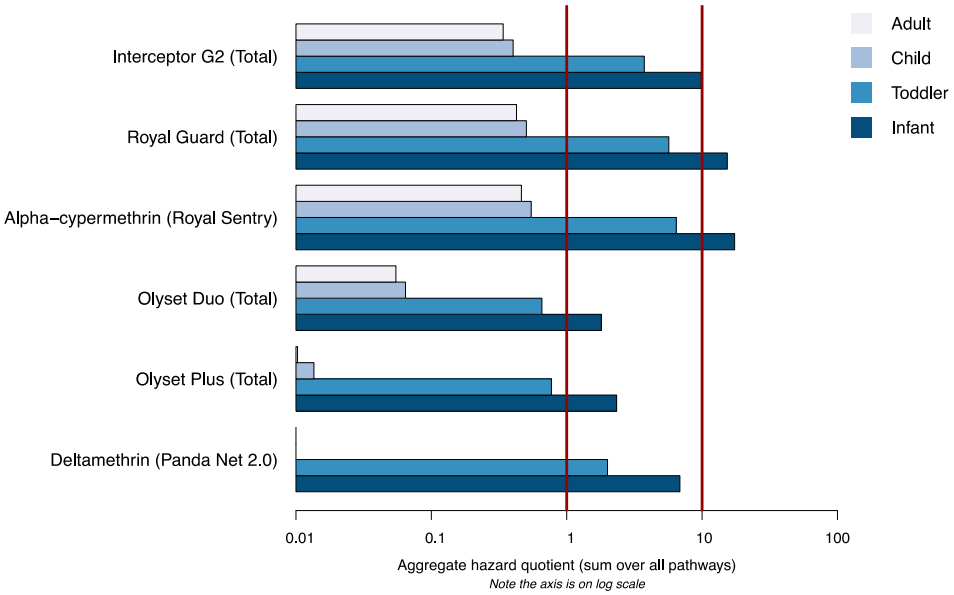
Table 4-2 presents the highest HQ and ILCR results for total exposure across all receptors for each product. Of the six LLIN products included in this update, five have screening risk estimates that suggest *some* potential for adverse noncancer health effects for the infant receptor. However, no HQ was above a value of 20 and given the level of conservatism, particularly the underlying assumptions in screening infant exposures, this suggests a low potential for adverse effects. The ILCR for lifetime exposure to permethrin (Olyset Duo and Olyset Plus) beginning as an infant was approximately 5E-04.

Table 4-2. Highest Risk Results for LLINs

ACTIVE INGREDIENT (PRODUCT)	HIGHEST RESULT	EXPOSURE SCENARIO
Alpha-cypermethrin and chlorfenapyr (Interceptor G2)	HQ = 9.8	**Noncancer hazard**: total exposure for the infant including dermal, inhalation, direct oral, hand-to-mouth, and breast milk
Alpha-cypermethrin and Pyriproxyfen (Royal Guard)	HQ = 15	**Noncancer hazard**: total exposure for the infant including dermal, inhalation, direct oral, hand-to-mouth, and breast milk
Alpha-cypermethrin (DCT Royal Sentry)	HQ = 17	**Noncancer hazard**: total exposure for the infant including dermal, inhalation, direct oral, hand-to-mouth, and breast milk
Permethrin and Pyriproxyfen (Olyset Duo)	HQ = 1.8 ILCR = 5E-04	**Noncancer hazard**: total exposure for the infant including dermal, inhalation, direct oral, hand-to-mouth, and breast milk **Cancer risk**: total lifetime exposure for the adult, child, toddler, and infant (assumes continuous lifetime exposure)
Permethrin and piperonyl butoxide (Olyset Plus)	HQ = 2.3 ILCR = 5E-04	**Noncancer hazard**: total exposure for the infant including dermal, inhalation, direct oral, hand-to-mouth, and breast milk **Cancer risk**: total lifetime exposure for the adult, child, toddler, and infant
Deltamethrin (Panda Net 2.0)	HQ = 6.8	**Noncancer hazard**: total exposure for the infant including dermal, inhalation, direct oral, hand-to-mouth, and breast milk

Figure 4-5 presents the risk assessment results for the five LLIN products aggregated across exposure scenarios for resident receptors. Because LLINs are factory-treated, there were no worker exposure scenarios that needed to be included under this intervention. The figure shows that the highest risk for all nets is predicted for the infant for the sleeping scenario, followed by the toddler, the child, and the adult receptors. The Olyset products have the least potential for adverse human health effects, with HQ values up to approximately a factor of 10 lower than other products. Infant exposures include multiple exposure routes including: (1) inhalation of insecticide in the zone around the net, (2) dermal contact with the net, (3) mouthing behavior on the net, (4) hand to mouth contact, and (5) via the ingestion of breast milk from a mother who is exposed by dermal and inhalation pathways. As shown in Annex C, the direct oral exposure by the infant (i.e., sucking on the net) clearly drives the HQ estimates. Dermal exposure as an adult, direct oral exposure (mouthing of the net) by infants and toddlers, and dermal exposures of toddlers and children are the main contributors to the ILCR of 5E-04.

Figure 4-5. Aggregate HQs – Chronic Exposure for Residents



4.2.1 HUMAN HEALTH RISK

For all products, the risk screening results for the washing scenarios were below the target HQ of 1 for all human receptors, generally by two or more orders of magnitude. Therefore, the focus of this section is exclusively on the results for the sleeping scenarios.

Figure 4-6 provides the risk profiles for each of the LLINs discussed in this section. These figures summarize all of the HQs calculated by the dermal, oral, and inhalation exposure routes for residential receptors.

Permethrin; cancer risk (Olyset Duo and Olyset Plus)—These products contain equivalent permethrin content and hence the cancer risk results apply to both. Although the calculated ILCR of 5E-04 is five times larger than the risk threshold described in Section 3.2, the many conservative assumptions and models suggest that even a reasonably conservative estimate of ILCR is likely to be less than 1E-04. As discussed in Section 3.2.3, lifetime cancer risk is reported for the individual, rather than by age cohort. In this case, potential exposures have been summed for the four age cohorts, protectively implying continuous exposure to a permethrin-containing net during a 50-year residential exposure duration. Significantly, the protective exposure assumptions applied to the exposure calculations for each age cohort are therefore all assumed to occur for a single hypothetical individual. For example, dermal contact with the net is protectively assumed to occur over one-third of the area of the hands and feet, arms, lower legs, and trunk (WHO LLIN GRAM, 2012) every single night of the individual's 50-year exposure duration. Additionally, infants and toddlers are assumed to mouth, chew or suck a 50-cm^2 area of the net each night, which is characterized as a worst-case assumption by the WHO (WHO LLIN GRAM, 2012).

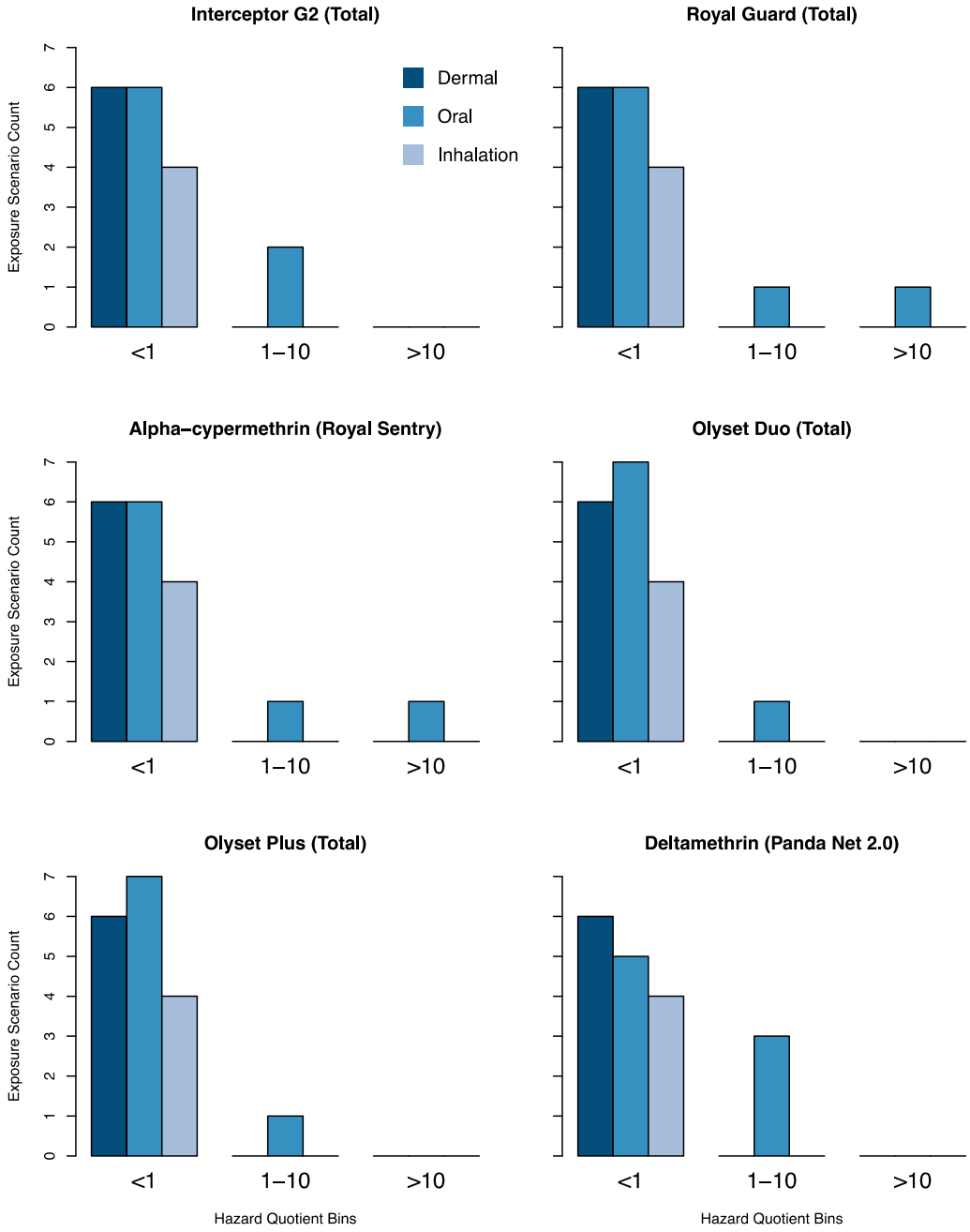
It should be noted that the USEPA has been involved in a review of all permethrin uses since June, 2011 (called registration review—docket USEPA-HQ-OPP-2011-0039), and expects to complete the registration review in 2017. In addition, in the USEPA's Integrated Risk Information System (IRIS), the Carcinogenicity Assessment for Lifetime Exposure is classified as "Not available at this time." After USEPA concludes its

evaluation of current research on permethrin and evidence of carcinogenicity, USAID will revisit the cancer risk assessments for permethrin and update as appropriate.

Alpha-cypermethrin and chlorfenapyr (Interceptor G2)—This product includes a synthetic pyrethroid (alpha-cypermethrin) and halogenated pyrrole (chlorfenapyr) referred to as a "pro-insecticide" because it must be metabolized to become active. Given the different mechanisms of action, the two insecticides in this product were considered to be additive, rather than synergistic, with regard to human health risk. Because both insecticides can induce neurological effects (albeit by different mechanisms) treating them as additive is reasonably conservative approach. USEPA's risk assessment of alpha-cypermethrin was updated in 2008, and the toxicological data used to derive human health benchmarks covers multiple exposure routes and durations. The data for chlorfenapyr (discussed above), although not evaluated recently by the USEPA, also provides a solid basis for benchmark derivation with respect to the types and duration of exposure. Given the quality of the toxicological database, and the fact that the risk estimates for both active ingredients are above the target HQ of 1, *some* potential for adverse effects for infants and toddlers is indicated if those receptors exhibit significant mouthing behaviors (per the exposure scenario). However, no HQ exceeded 10 and, therefore, the potential for neurological effects associated with this product is considered quite low. Infant and toddler total HQ results are largely related to the direct oral exposure pathway, where infants and toddlers are assumed to assumed to mouth, chew or suck a 50-cm^2 area of the net each night, which is characterized as a worst-case assumption by the WHO (WHO LLIN GRAM, 2012).

Alpha-cypermethrin and pyriproxyfen (Royal Guard)—This product is treated with a synthetic pyrethroid (alpha-cypermethrin) and a pyridine-based insecticide (pyriproxyfen). As with Interceptor G2, these active ingredients work via very different mechanisms of action, and the assumption of additivity is highly conservative in that any effects on human health would be expected to involve different systems and endpoints. The highest HQ for Royal Guard was estimated for alpha-cypermethrin for the infant (15) over all exposure pathways; this result was quite similar to the risk estimate for DCT Royal Sentry discussed below. The contribution to risk from pyriproxyfen was negligible. The risk profile for Royal Guard is very similar to the risk profile for Interceptor G2 and DCT Royal Sentry; this is not surprising given the fact that all three products contain alpha-cypermethrin at similar levels. The results are suggestive of *some* potential for adverse health effects (primarily for neurotoxicity) for both the dermal route of exposure (all receptors) and oral route of exposure (toddler and infant). Infant and toddler total HQ results are largely related to the direct oral exposure pathway, where infants and toddlers are assumed to mouth, chew or suck a 50-cm^2 area of the net each night, which is characterized as a worst-case assumption by the WHO (WHO LLIN GRAM, 2012).

Figure 4-6. Risk Profile for Residents – LLINs



Alpha-cypermethrin (DCT Royal Sentry)—The concentration of the active ingredient in this product is very similar to the concentration in Interceptor G2 and Royal Guard. Not surprisingly, the risk profile shown in Figure 4-6 looks very similar across all LLINs that contain alpha-cypermethrin. Therefore, the previous discussions regarding the potential for adverse health effects of alpha-cypermethrin are applicable to Royal Sentry.

Permethrin and pyriproxyfen (Olyset Duo)—This product includes a synthetic pyrethroid (permethrin) and a pyridine-based insecticide (pyriproxyfen). As with Interceptor G2 and Royal Guard, these active

ingredients work via very different mechanisms of action. Thus, for this product, the assumption of additivity is highly conservative in that any effects on human health would be expected to involve different systems and endpoints. Given the small exceedance (1.8) of the target HQ, the Olyset Duo net is judged to present minimal noncancer risk to human health.

Permethrin and piperonyl butoxide (Olyset Plus)—This product includes the synthetic pyrethroid (permethrin) and a synergist, PBO, a widely-used insecticide synergist that acts by protecting the co-applied insecticide (e.g., pyrethrins, pyrethroids) from metabolic attack by inhibiting an enzyme system that catalyzes oxidative processes in living systems. As discussed in Section 3, a simple and protective additive approach for HQs was used for the different pesticides in a product. Given the small exceedance (2.3) of the target HQ, the Olyset Plus net is judged to present minimal noncancer risk to human health.

Deltamethrin (Panda Net 2.0)—Deltamethrin is a synthetic pyrethroid that is incorporated into polyethylene in the Panda Net 2.0. The mechanism of action is the same as for alpha-cypermethrin, which explains why the risk profile in Figure 4-5 for Panda Net 2.0 is similar to the other LLINs containing synthetic pyrethroids (Interceptor G2, Royal Guard, and Royal Sentry). The majority of screening HQ values for Panda Net 2.0 were below the target HQ although, as with the other LLINs, the toddler and infant receptors both had HQ exceedances above 1 though below 10, suggesting *some* potential for adverse neurological effects.

4.2.2 CONCLUSIONS

Taken together, the LLINs have relatively similar risk profiles because four of the six products contain synthetic pyrethroids (Interceptor G2, Royal Guard, Royal Sentry, and Panda Net 2.0). In general, the toxicology of these pyrethroids is well known (three products contain alpha-cypermethrin), and the association with neurological effects is well established. Thus, based on the conservative exposure scenarios, there is *some* potential for adverse health effects, specifically, for infants and toddlers that engage in significant mouthing behavior with the nets. However, there are several sources of uncertainty that tend to bias the risk results towards the overestimation of risk. Notably, the amount of pesticide that could actually be dislodged during mouthing is highly uncertain, and is likely to be significantly less than the conservative default of 33% recommended in the GRAM (WHO LLIN GRAM, 2012). This value was recommended by the WHO for "conventional" treated nets in the 2012 GRAM, but the factory treatment of LLINs is likely to reduce that value significantly. Morever, infants are usually placed under the center of LLINs, alongside their mothers, further reducing the risk of direct sucking of LLINs. If there is sucking behavior, it is not likely to in a unique section every night, reducing the actual mass of insecticide that is available during the service lifetime of the net. As discussed in Section 4.2.1, the conservative default assumptions related to mouthing have a significant impact on the risk results, and the actual risk to infants and toddlers is likely to be much less. Simply dropping the percent of dislodgeable pesticide to 10% would reduce all HQs to single digits, and this is just one of the several protective assumptions discussed. Based on these calculations, and the level of conservatism described in the exposure models, it is considered likely that actual risks are likely to be below threshold values. For this reason, and because of the efficacy of LLINs in malaria vector control, potential adverse health risks related to LLINs are considered to be acceptable.

4.3 LARVICIDING

Table 4-3 presents the highest HQ results for chemical larvicides based on total estimated exposure. This includes worker exposures associated with mixing/loading and spraying, as well as residential exposures due to dermal contact and ingestion of groundwater that may have been contaminated with larvicides. As shown in Table 4-3, the HQs for larvicides are all below the target HQ of 1, with most screening HQs several orders of magnitude below the target HQ. Lifetime incremental cancer risk is also well below the significance threshold of 1E-04.

Table 4-3. Highest Risk Results for Larviciding

ACTIVE INGREDIENT (PRODUCT)	HIGHEST RESULT	EXPOSURE SCENARIO
Chlorpyrifos	HQ = 0.00035	**Noncancer hazard**: total worker exposure (no PPE)
Diflubenzuron (DT)	HQ = 0.00012	**Noncancer hazard**: total worker exposure (no PPE)
Diflubenzuron (G)	HQ = 0.00012	**Noncancer hazard**: total worker exposure (no PPE)
Diflubenzuron (WP)	HQ = 0.00018	**Noncancer hazard**: total worker exposure (no PPE)
Diflubenzuron (4-chlorophenylurea metabolite)	ILCR =6E-09	**Cancer Risk**: total lifetime exposure for the adult, child, toddler, and infant (groundwater; assumes continuous lifetime exposure)
Fenthion	HQ = 0.24	**Noncancer hazard**: total worker exposure (no PPE)
Methoprene	HQ = 0.000015	**Noncancer hazard**: total worker exposure (no PPE)
Novaluron	HQ = 0.0046	**Noncancer hazard**: total worker exposure (no PPE)
Pirimiphos-methyl	HQ = 0.36	**Noncancer hazard**: total worker exposure (no PPE)
Pyriproxyfen	HQ = 0.000073	**Noncancer hazard**: total worker exposure (no PPE)
Spinosad	HQ = 0.00018	**Noncancer hazard**: toddler ingestion exposure
Spinosad 83.3 Monolayer	HQ = 0. 00018	**Noncancer hazard**: toddler ingestion exposure
Spinosad 25 Ext. Release	HQ = 0.00015	**Noncancer hazard**: toddler ingestion exposure
Temephos (EC)	HQ = 0.072	**Noncancer hazard**: total worker exposure (no PPE)
Temephos (G)	HQ = 0.070	**Noncancer hazard**: total worker exposure (no PPE)

4.3.1 HUMAN HEALTH RISK

Given screening results presented in Table 4-3, which are all far below threshold criteria, there is no need to present the aggregate HQ figures or the risk profiles for the chemical insecticides.

Instead, this section provides a discussion of the potential health risks associated with the use of biological larvicides. Although this class of larvicide is widely regarded as safe with regard to human health effects, we have summarized information pertinent to the safe use of biological larvicides, specifically, *Bacillus thuringiensis israelensis* or, simply, Bt.

Relevant Biology. Bt is a facultative anaerobic, motile, spore-forming, gram-positive. It has been isolated from soils, leaf surfaces, and aquatic environments. Bt is genetically indistinguishable from *Bacillus cereus* (Bc), except for the ability of Bt to produce parasporal crystalline inclusions, which are toxic for certain invertebrates. The parasporal inclusions are formed by different insecticidal crystal proteins (ICP). ICP acts subsequent to solubilization in the midgut of the insect larva, followed by the conversion of the protoxin to the biologically active toxin by proteolytic enzymes. (WHO 1999; WHO 2012)

During vegetative growth, some Bt strains are capable of producing an assortment of toxins, including Bc toxins. Of particular note is beta-exotoxin, a heat-stable nucleotide which inhibits the enzyme ribonucleic acid (RNA) polymerase. Specifically, *Bacillus thuringiensis* isolates may produce a beta-exotoxin called thuringiensin (USEPA 1998). Because RNA synthesis is a vital process in all life, beta-exotoxin is toxic towards almost all forms of life, including humans. The development of pure cultures of Bt that do not produce beta-exotoxin and monitoring to ensure this purity is a primary method of ensuring the toxicological safety of Bt insecticides. (USEPA 1998; WHO 2012)

After the application of Bti to an ecosystem, the vegetative cells and spores may persist, at gradually decreasing concentrations, for weeks, months or years as a component of the natural microflora. However, the ICPs associated with the spores are rendered biologically inactive within hours or days. (WHO 1999; WHO 2012)

The U.S. Environmental Protection Agency (1998) notes that the genetic material encoding the ICP can be moved among subspecies of Bt using genetic engineering techniques to provide different host spectrum ranges related to the various subspecies. Therefore, specific strains (pure cultures descended from one isolation) rather than subspecies taxonomic designations such as *israelensis* are used by USEPA for pesticide registration purposes.

Physical form and application. "…small pale brown granules intended for spray application after disintegration and dispersion in water, or for direct application to mosquito larval habitats including water storage containers." (WHO 2012) "Bt AM65-52 is used in public health applications, to control the larvae of mosquitoes and black flies, the adults of which are disease vectors." "Generally, Bt formulations may be applied foliage, soil, aquatic environments, and food- or water-storage facilities. Formulated as water-dispersible granules, Bti AM65-52 is intended for mosquito control in potable or non-potable water and may be dispersed in water before or after application." (WHO 2012) "Most Bt products contain both ICP and viable spores, but in some Bti products the spores are inactivated." (WHO 1999)

Toxicology. The Registration Eligibility Decision (RED) fact sheet distributed by USEPA (1998) summarizes the toxicity and pathogenicity of Bt pesticides with this statement:

> *To date, no known mammalian health effects have been demonstrated in any infectivity/pathogenicity study. Some strains of Bacillus thuringiensis have the potential to produce various toxins that may exhibit toxic symptoms in mammals, however the manufacturing process includes monitoring to prevent these toxins from appearing in products.*

This summary statement is rendered in more specific terms in relation to the regulatory environment for pesticides in the U.S. in the Human Health Assessment discussion in USEPA (1998):

> *The sum total of all toxicology data submitted to the Agency complete with the lack of any reports of significant human health hazards of the various Bacillus thuringiensis strains allow the conclusion that all infectivity/pathogenicity studies*

normally required under 40 Code of Federal Regulations, Part 158, for the use patterns of the registered products be waived in the future as long as product identity and manufacturing process testing data indicated there is no mammalian toxicity associated with the strain.

As noted in the summary of Bt biology, *Bacillus thuringiensis* isolates may produce a heat stable beta-exotoxin called thuringiensin (USEPA 1998). The development of pure cultures of Bti that do not produce beta-exotoxin and monitoring to ensure this purity is a primary method of ensuring the toxicological safety of Bti insecticides. (USEPA 1998; WHO 2012)

The U.S. Environmental Protection Agency promulgates tolerances for the residues of different pesticides on agricultural commodities and foods. The USEPA 1998 notes that Bt is exempted from the requirements for a tolerance on beeswax and honey and all other raw agricultural commodities when it is applied either to growing crops, or post-harvest in accordance with good agricultural practices. This tolerance exemption is promulgated in 40 Code of Federal Regulations (CFR) §180.1011.

No known toxins or metabolites of Bt have been identified as immune system toxicants (USEPA 1998). A subsequent study of immune responses to farm workers exposed in 1995 to Bt pesticides determined that positive skin-prick tests and immunoglobulin antibody responses to extracts of Bt spores and vegetative cells were statistically associated with higher levels of Bt exposure (Bernstein et al, 1999). However, the study did not find evidence of occupationally related respiratory symptoms such as asthma. The possibility of exotoxin or other contamination in the Bt pesticides applied in 1995 is indeterminate, so the relevance of this study to modern Bt pesticides is unclear.

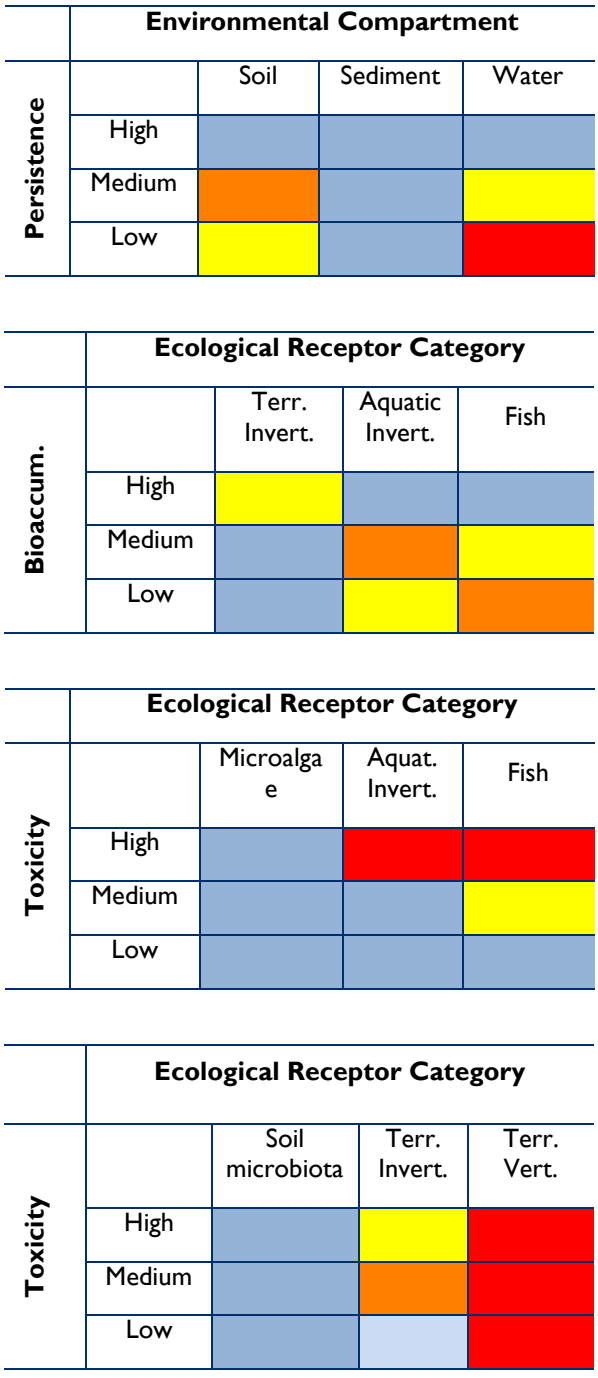
4.3.2 CONCLUSIONS

Based on the results of the risk screening of chemical larvicides and the qualitative information on potential health impacts associated with biological larvicides, both classes of larvicides are considered safe for their intended uses.

4.3.3 ECOLOGICAL RISK

Annex E provides additional details regarding the environmental behavior and potential toxicity to non-target organisms. In this section, Figures 4-7 through 4-15 present heat maps of each of the chemical larvicides; these heat maps provide a visual representation of the environmental persistence, bioaccumulation potential, and toxicity to organisms in aquatic and terrestrial ecosystems. The heat maps use grey to indicate the absence of data, and use warmer colors to indicate that more data were identified in a particular category, with yellow<orange<red. When warm colors are evident in the high, medium, and low categories (looking down the column), this indicates significant variability in the data related to the environmental behavior or toxicity of the larvicide. When warm colors are concentrated in one, or possibly, two adjacent categories, this indicates that the data are less variable across different studies.

Figure 4-7. Ecological Risk Profile - Chlorpyrifos



Chlorpyrifos undergoes photodegradation and biodegradation in soil, with an expected half-life of 1 to 2 weeks in surface soil. Biodegradation in water is also important, with an expected half-life of 3 weeks or longer. In water, it adsorbs to suspended solids and sediment.

The bioaccumulation potential for chlorpyrifos in aquatic invertebrates and fish is low to moderate. A limited number of studies indicate chlorpyrifos has a high bioaccumulation potential in terrestrial invertebrates.

Chlorpyrifos is moderately to highly toxic to fish, and also highly toxic to aquatic invertebrates.

The terrestrial toxicity profile for chlorpyrifos suggests a high degree of variability in its toxicity to different terrestrial vertebrates. It is moderately to highly toxic to terrestrial invertebrates.

Figure 4-8. Ecological Risk Profile - Diflubenzuron

	Environmental Compartment			
Persistence		Soil	Sediment	Water
	High			
	Medium			
	Low			

Diflubenzuron undergoes photodegradation and biodegradation in soil. It also biodegrades in the water environment, with a half-life of approximately 2 to 4 weeks, and is expected to adsorb to suspended solids and sediment.

	Ecological Receptor Category			
Bioaccum.		Terr. Invert.	Aquatic Invert.	Fish
	High			
	Medium			
	Low			

The potential for diflubenzuron to bioaccumulate in aquatic invertebrates and fish is low. A limited number of studies indicate diflubenzuron has a low bioaccumulation potential in terrestrial invertebrates.

	Ecological Receptor Category			
Toxicity		Microalgae	Aquat. Invert.	Fish
	High			
	Medium			
	Low			

Diflubenzuron has low toxicity to fish and microalgae. The data reviewed indicate a predominantly low to moderate toxicity to aquatic invertebrates.

	Ecological Receptor Category			
Toxicity		Soil microbiota	Terr. Invert.	Terr. Vert.
	High			
	Medium			
	Low			

Diflubenzuron has a low degree of toxicity to terrestrial vertebrates, and low to moderate toxicity to terrestrial invertebrates.

Figure 4-9. Ecological Risk Profile - Fenthion

	Environmental Compartment		
Persistence	Soil	Sediment	Water
High			
Medium			
Low			

Fenthion undergoes photodegradation and biodegradation in soil and water. It is expected to adsorb to suspended solids and sediment in water. It has an expected half-life of about 5 weeks in soil and <1 to 3 weeks in water.

	Ecological Receptor Category		
Bioaccum.	Terr. Invert.	Aquatic Invert.	Fish
High			
Medium			
Low			

The data reviewed suggest that fenthion has a predominantly low tendency to bioaccumulate in fish, but limited data indicate high potential. Limited data indicate it has a moderate bioaccumulation potential in aquatic invertebrates and high potential in terrestrial invertebrates.

	Ecological Receptor Category		
Toxicity	Microalgae	Aquat. Invert.	Fish
High			
Medium			
Low			

Fenthion is moderately to highly toxic in fish and moderately toxic to aquatic invertebrates.

	Ecological Receptor Category		
Toxicity	Soil microbiota	Terr. Invert.	Terr. Vert.
High			
Medium			
Low			

Fenthion is highly toxic to terrestrial invertebrates. It is moderately to highly toxic to terrestrial vertebrates.

Figure 4-10. Ecological Risk Profile - Methoprene

	Environmental Compartment		
Persistence	Soil	Sediment	Water
High			
Medium			
Low			

Methoprene binds tightly to soil and is practically insoluble in water. It is rapidly broken down in soil, with a half-life of 1 to 2 weeks. Methoprene also rapidly photodegrades in water, with a half-life of 1 to 2 days, but may persist for longer than 4

	Ecological Receptor Category		
Bioaccum.	Terr. Invert.	Aquatic Invert.	Fish
High			
Medium			
Low			

Limited data indicate a high potential for methoprene to bioaccumulate in aquatic and terrestrial invertebrates is high. It has a low to moderate potential to bioaccumulate in fish.

	Ecological Receptor Category		
Toxicity	Microalgae	Aquat. Invert.	Fish
High			
Medium			
Low			

The preponderance of data indicate methoprene is moderately toxic to fish. Methoprene is highly toxic to aquatic insects and crustaceans, but only slightly toxic in molluscs.

	Ecological Receptor Category		
Toxicity	Soil microbiota	Terr. Invert.	Terr. Vert.
High			
Medium			
Low			

Methoprene exhibits low toxicity for terrestrial vertebrates and invertebrates.

Figure 4-11. Ecological Risk Profile - Novaluron

	Environmental Compartment			
Persistence		Soil	Sediment	Water
	High			
	Medium			
	Low			

Novaluron is relatively resistant to both photolysis and hydrolysis. It's half-life in soil is highly variable, being approximately 1 to 13 weeks. It is expected to be relatively persistent in aquatic environments.

	Ecological Receptor Category			
Bioaccum.		Terr. Invert.	Aquatic Invert.	Fish
	High			
	Medium			
	Low			

The potential for bioaccumulation of novaluron to in both terrestrial and aquatic invertebrates and fish is high. Studies indicate a high potential for persistence in the aquatic food chain.

	Ecological Receptor Category			
Toxicity		Microalgae	Aquat. Invert.	Fish
	High			
	Medium			
	Low			

Novaluron is highly toxic to microalgae, fish and aquatic invertebrates.

	Ecological Receptor Category			
Toxicity		Soil microbiota	Terr. Invert.	Terr. Vert.
	High			
	Medium			
	Low			

Novaluron exhibits low toxicity to terrestrial vertebrates and invertebrates.

Figure 4-12. Ecological Risk Profile - Pirimiphos-methyl

	Environmental Compartment			
Persistence		Soil	Sediment	Water
	High			
	Medium			
	Low			

Pirimiphos-methyl has limited mobility and persistence in soil. It hydrolyzes rapidly in acidic soils, but is more stable in neutral and alkaline soils with a half-life of about 1 week. It decomposes in sunlight, with a half-life of 1 day, and also degrades in water by hydrolysis.

	Ecological Receptor Category			
Bioaccum.		Terr. Invert.	Aquatic Invert.	Fish
	High			
	Medium			
	Low			

Limited data indicate that pirimiphos-methyl has low toxicity to fish, moderate toxicity to aquatic invertebrates, and high toxicity to terrestrial vertebrates.

	Ecological Receptor Category			
Toxicity		Microalgae	Aquat. Invert.	Fish
	High			
	Medium			
	Low			

Pirimiphos-methyl is moderately to highly toxic to fish and highly toxic to aquatic invertebrates. However, the preponderance of data indicate that it has low toxicity to microalgae.

	Ecological Receptor Category			
Toxicity		Soil microbiota	Terr. Invert.	Terr. Vert.
	High			
	Medium			
	Low			

Pirimiphos-methyl is not expected to pose a hazard to birds and mammals, but laboratory studies indicate it is highly toxic to birds. It is highly toxic to honeybees and other terrestrial invertebrates.

Figure 4-13. Ecological Risk Profile – Pyriproxyfen

	Environmental Compartment			
Persistence		Soil	Sediment	Water
	High			
	Medium			
	Low			

Pyriproxyfen has a half-life of approximately 1 week in aerobic soil. It sorbs strongly to organic matter and, due to its low mobility, it can persist in anaerobic environments. In aerobic aquatic environments, it has a half-life of 2 to 3 weeks.

	Ecological Receptor Category			
Bioaccum.		Terr. Invert.	Aquatic Invert.	Fish
	High			
	Medium			
	Low			

Pyriproxyfen can accumulate in lipids and, based on a log Kow value of 5.6, there is potential for accumulation in the aquatic food chain (particularly in anaerobic environments). No data were found related to bioaccumulation in terrestrial systems.

	Ecological Receptor Category			
Toxicity		Microalgae	Aquatic Invert.	Fish
	High			
	Medium			
	Low			

At rates typical of mosquito control programs (<50 ppb), pyriproxyfen is not expected to adversely affect the majority of fish and aquatic invertebrates. However, studies have shown that at higher concentrations, pyriproxyfen exhibits significant toxicity to microalgae, aquatic invertebrates, and fish.

	Ecological Receptor Category			
Toxicity		Soil microbiota	Terr. Invert.	Terr. Verts.
	High			
	Medium			
	Low			

The terrestrial toxicity profile for pyriproxyfen suggests low toxicity to birds, mammals, and invertebrates. It is practically non-toxic to bees, and is minimally toxic to earthworms.

Figure 4-14. Ecological Risk Profile - Spinosad

	Environmental Compartment			
Persistence		Soil	Sediment	Water
	High			
	Medium			
	Low			

Spinosad degrades rapidly in the environment. It is susceptible to microbial degradation (particularly under aerobic conditions) and photolysis in sunlight. Half-lives in the water column are short, but it could persist on sediments that are unexposed to sunlight.

	Ecological Receptor Category			
Bioaccum.		Terr. Invert.	Aquatic Invert.	Fish
	High			
	Medium			
	Low			

Available studies suggest that spinosad does not bioaccumulate in aquatic organisms, particularly in fish. Thus, there is very little potential for aquatic food chain effects. Data indicate a potential for bioaccumulation in terrestrial invertebrates.

	Ecological Receptor Category			
Toxicity		Micro-algae	Aquatic Invert.	Fish
	High			
	Medium			
	Low			

The aquatic toxicity profile of spinosad indicates that it has moderate to low acute toxicity to most aquatic organisms. However, data suggest that chronic exposures are likely to be more toxic to aquatic invertebrates than fish.

	Ecological Receptor Category			
Toxicity		Soil microbiota	Terr. Invert.	Terr. Verts.
	High			
	Medium			
	Low			

The terrestrial toxicity profile of spinosad suggests that is practically non-toxic to mammals and birds. Spinosad can be highly toxic to bees; however, once the liquid spray residues are allowed to dry for up to three hours, it is not harmful to foraging honeybees or bumblebees.

Figure 4-15. Ecological Risk Profile - Temephos

	Environmental Compartment			
Persistence		Soil	Sediment	Water
	High			
	Medium			
	Low			

Temephos has a low water solubility and a high affinity for soil, and therefore is not extremely mobile in the soil. Temephos adsorbs rapidly to organic media and is quickly degraded by photolysis and microbial action. However, it can be persistent in aquatic systems in their absence.

	Ecological Receptor Category			
Bioaccum.		Terr. Invert.	Aquatic Invert.	Fish
	High			
	Medium			
	Low			

Temephos is a hydrophobic chemical and more likely to bind to fatty substances, therefore it has a high bioaccumulation potential.

	Ecological Receptor Category			
Toxicity		Microalgae	Aquat. Invert.	Fish
	High			
	Medium			
	Low			

Temephos is slightly to moderately toxic to fish, and is moderately to highly toxic to aquatic invertebrates.

	Ecological Receptor Category			
Toxicity		Soil microbiota	Terr. Invert.	Terr. Vert.
	High			
	Medium			
	Low			

Temephos is not expected to have a direct effect on terrestrial animals since it is applied to water, so exposure is limited. However, it is toxic to some bird species and exhibits varying toxicity to other terrestrial vertebrates. It is highly toxic to honeybees.

4.3.4 CONCLUSIONS

The ecological risk profiles presented in this section show that there is wide variability in the persistence, bioaccumulation potential, and toxicity to aquatic and terrestrial ecosystems. The selection of an appropriate larvicide should consider the environmental behavior and the potential toxicity of the larvicide, as well as the ecological values associated with the area or areas designated for treatment. For instance, if a small waterbody or wetland had specific value as a fisheries habitat, a larvicide such as pyriproxyfen would be a relatively poor choice given its persistence in water and high toxicity to aquatic organisms, including fish.

4.4 INSECTICIDE TREATED CLOTHING

Permethrin is the only insecticide that is USEPA-approved for treated clothing, and is the only insecticide under consideration by USAID for this intervention. As stated in Section 2.0, permethrin-treated clothing has been used for over 20 years in the military and, since 2003, permethrin-treated clothing has been registered and approved by the USEPA. Factory-treated clothing as well as treatment kits are readily available from a wide variety of wholesale vendors and retailers. Factory-treated clothing is believed to be the most likely intervention; however, clothing treated with kits or sprays were also considered.

4.4.1 HUMAN HEALTH RISK

The USEPA's comprehensive human health risk assessment was reviewed for all registered uses in 2006, as well as its subsequent review of factory-treated exposure scenarios, including short-term and long-term cancer risks to adults, children, and toddlers wearing permethrin-treated clothing, conducted in 2009. The risk assessment methodology included dermal and incidental ingestion exposures for workers and resident receptors included in the HAARP. The USEPA is considered an expert agency in the conduct of health and environmental risk assessment, and therefore, the purpose of this review was to determine whether the exposure scenarios were consistent with HAARP and suitable to support decision making for the malaria vector control program. It was determined that the USEPA's risk assessment methodology—risk assessment algorithms, inputs, and simplifying assumptions—was consistent with the HAARP with minor exceptions. Notably, the USEPA did not include the breast milk pathway. However, permethrin is readily metabolized in the mammalian liver, and available information suggests that the half-life in the body is on the order of hours, rather than days. Therefore, the breast milk pathway would be expected to be insignificant. The USEPA's conclusion was that none of the exposure scenarios included in the risk assessment posed significant immediate or long-term risks to people wearing factory treated clothing.

4.4.2 CONCLUSIONS

The long history of using permethrin-treated clothing by the military, the availability of factory-treated clothing and treatment kits, and the high relevance of the USEPA's risk assessment of permethrin-treated clothing support USAID's conclusion that this intervention is safe for use. For best results, studies suggest that the treated-clothing cover as much skin as possible; consequently, treated long-sleeved shirts and pants are recommended (Orseborne et al., 2016). Manufacturers suggest that permethrin-treated clothing be washed separately from other, non-treated garments. This recommendation would reduce dermal exposure (and possible hand-to-mouth exposure) with permethrin, particularly if the clothing is hand washed. Permethrin has not been associated with any reproductive, developmental, or teratogenic effects, and the research linking permethrin to cancer is, at present, equivocal. However, the concentration of permethrin in wash water would be expected to be quite low especially for factory-treated clothing. Given the poor dermal absorption of permethrin, this exposure scenario would not be expected to pose significant health risks.

4.5 LONG-LASTING INSECTICIDAL HAMMOCKS

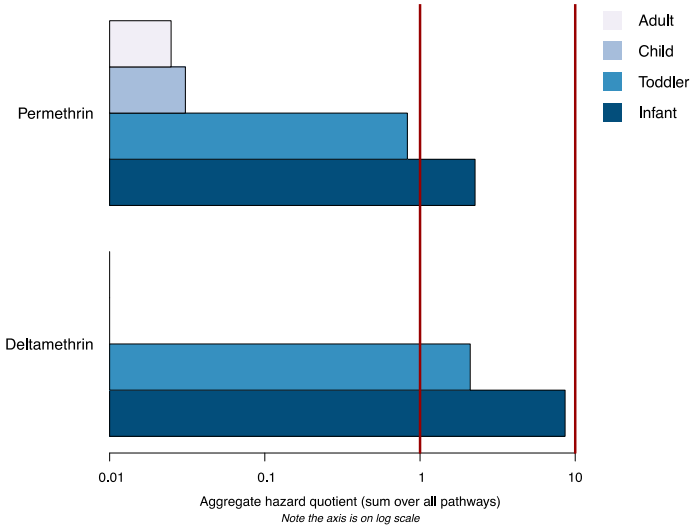
Insecticide treated hammocks, including LLIHs that are factory treated with permethrin or deltamethrin (e.g., Permanet 2.0 in the hammock shape), are included in this revised PEA. Permethrin has been approved by the USEPA for treatment of camping gear, including hammocks, including factory-treated LLIHs (e.g., DawaPlus Canopy Hammock) as well as the use of permethrin sprays to treat hammocks. **Table 4-4** presents the highest HQ results for total exposure across all receptors. The noncancer hazard HQs for both insecticides are above the target HQ of 1, suggesting *some* potential for adverse health effects for the infant receptor. In addition, the lifetime incremental cancer risk for permethrin-treated hammocks is above the target cancer risk of 1 in 10,000. The potential for noncancer effects or cancer is considered extremely low for the washing as evidenced by the HQs and ILCRs in Annex C for this scenario.

Table 4-4. Highest Risk Results for Permethrin-treated Hammocks

ACTIVE INGREDIENT (PRODUCT)	HIGHEST RESULT	EXPOSURE SCENARIO
Permethrin	HQ = 2.3	**Noncancer hazard**: total exposure for the infant, including dermal, direct oral, hand-to-mouth, and breast milk (sleeping)
Permethrin	ILCR = 2E-03	**Cancer risk**: total lifetime cancer risk for the adult, child, toddler, and infant (assumes continuous lifetime exposure) (sleeping)
Deltamethrin	HQ = 8.6	**Noncancer hazard**: total exposure for the infant, including dermal, direct oral, hand-to-mouth, and breast milk (sleeping)

Figure 4-16 compares the risk assessment results for the two treated hammock products across exposure scenarios for residential uses, assuming that the hammocks are factory treated. Similar to LLINs containing synthetic pyrethroid, the greatest contributor to the total HQ for infants and toddlers is mouthing behavior.

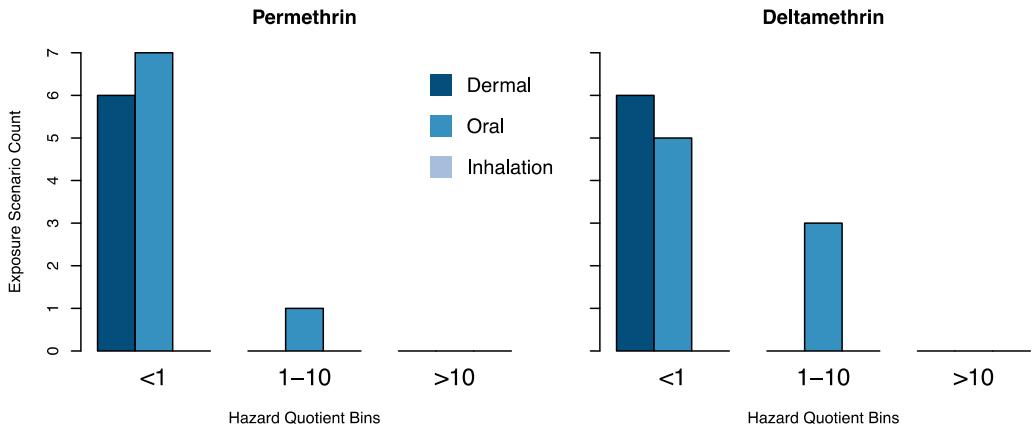
Figure 4-16. Aggregate HQs – Chronic Exposure for Residents



4.5.1 HUMAN HEALTH RISK

Noncancer hazards (acute and chronic) and the lifetime incremental cancer risk (permethrin only) for resident exposures during sleeping and washing scenarios were generated for LLIHs. Dermal contact and incidental ingestion via hand-to-mouth were also included; however, inhalation exposure was not evaluated because (1) not all LLIHs have LLINs attached, and (2) LLIHs are typically used outdoors where the air concentrations would be expected to be very low. Although no information on washing practices was identified for treated hammocks, it was anticipated that the outdoor use of hammocks would require periodic washing. **Figure 4-17** shows that the risk profiles for treated hammocks are very similar to the risk profiles for LLINs, except that the inhalation route was excluded. As with LLINs, the most significant exposure pathways contributing to lifetime cancer risk were dermal absorption and, for the infant and toddler, mouthing behavior.

Figure 4-17. Risk Profile for Residential Use of Hammocks



Permethrin—This active ingredient is a synthetic pyrethroid that, as discussed under the treated clothing intervention, has been approved by the USEPA for a wide variety of uses. One of the screening HQs for noncancer effects was *slightly* above the target HQ of 1, suggesting very low potential for risk.

Although the calculated ILCR of 2E-03 is twenty times larger than the risk threshold described in Section 3.2, the many conservative assumptions and models suggest that even a reasonably conservative estimate of ILCR is likely to be less than 1E-04. Because the exposure models for LLINs and LLIHs have many similar conservative assumptions, the reader is directed to Section 4.2.1 for a summary of the intentional protective biases related to the cancer risk assessment for permethrin.

As discussed in relation to LLIN cancer risks, USEPA has been involved in a review of all permethrin uses since June, 2011 (called registration review—docket USEPA-HQ-OPP-2011-0039), and expects to complete the registration review in 2017. After USEPA concludes its evaluation of current research on permethrin and evidence of carcinogenicity, USAID will revisit the cancer risk assessments for permethrin and update as appropriate.

Deltamethrin—Like permethrin, deltamethrin is a synthetic pyrethroid with the same mechanism of action. The HQs for oral exposure for infants and toddlers (mouthing the hammock) are somewhat higher than permethrin (e.g., 8.6 versus 2.3 for the infant) because deltamethrin is considerably more toxic than permethrin via the oral route of exposure. Even with the higher toxicity, the lower treatment concentration only results in about a 4-fold increase in the HQ relative to permethrin.

4.5.2 CONCLUSIONS

As suggested by the aggregate HQ figure (Figure 4-16), the risk profile (Figure 4-17), and the highest risk results table (Table 4-4), direct oral contact (infant and toddler HQ; ILCR) and dermal contact (ILCR) drive the risk assessment results estimates for the sleeping scenario. The sleeping exposure scenario is considered to be similarly conservative for hammocks and nets because:

1. relatively high values were assumed for skin surface area in contact with the hammock and net,
2. roughly 33% of the active ingredient is assumed to be available for release (as with LLINs), and
3. protective assumptions were applied for the fraction of residue that can be translodged onto the skin.

Several of these conservative assumptions are default values from the WHO GRAM for LLINs. For cancer risk, the adult is assumed to sleep in the same hammock every day, with no decrease in the concentration through time, and the exposure model implicitly assumes that a new hammock will be available as the old hammock approaches the end of its life cycle for the entire exposure duration. Thus, these risk estimates should be considered as an upper bound of the risk distribution. Additional information on adherence and usage characteristics would support reducing the level of conservatism in the screening, and improve the accuracy of the results.

While the aggregate HQs were at or above 1, but less than 10, for toddlers and infants for both deltamethrin- and permethrin-treated hammocks, LLIHs are not targeted to these two groups, and thus infants and toddlers and not likely to be sleeping in LLIHs. The protective assumption that infants and toddlers will use LLIHs contributes to the unrealistically high LLIH cancer risks. If only children and adult exposures are considered, the ILCR results is 5E-04.

USAID is thus recommending permethrin- and deltamethrin-treated hammocks at or below the concentrations specified in this PEA as safe interventions.

5.0 ENVIRONMENTAL MANAGEMENT RESPONSE

Human health and environmental mitigation activities are intended to reduce adverse human health and environmental impacts that result from interventions. Mitigation measures can be categorized into the following types of actions: avoid impact, minimize or diminish effects, rectify or repair by rehabilitation, reduce or eliminate over time, or provide compensation. Monitoring is conducted to determine when mitigation is necessary and whether or not mitigation is working successfully. During implementation of the intervention, monitoring can identify negative human health or environmental impacts in time for mitigation measures to be adjusted or additional measures put in place. Therefore, monitoring is a necessary complement to the mitigation of negative human health and environmental impacts. Additionally, 22 CFR 216.3(a)(8) says that, "To the extent feasible and relevant, projects and programs for which Environmental Impact Statements or Environmental Assessments have been prepared should be designed to include measurement of any changes in the environmental quality, positive or negative, during their implementation".

The following section contains recommended mitigation measures for any insecticide-based vector control intervention and for the intervention-specific vector control interventions of LLINs, IRS, and larviciding. While these mitigation measures represent best practices, host-country stakeholders should be involved in reviewing proposed mitigation and monitoring activities to ensure they are technologically appropriate, culturally suitable, and feasible. Mitigation and monitoring activities should then be adapted to the host-country situation without compromising human health and the environment, and reflected in the tiered environmental documents (i.e., SEAs, IEEs, etc.). The following sections also summarize progress made in addressing previous PEAs' mitigation measures and policy decisions made since the last PEA update.

Mitigation measures by intervention, responsibilities for implementation, and monitoring and reporting measures and frequency should be captured in Environmental Mitigation and Monitoring Plans (EMMPs). These plans, which should be provided to management teams, serve as the tool for ensuring adherence to mitigation and monitoring practices and are incorporated into work plans and budgets. Projects are required to track EMMP implementation.

Environmental Mitigation and Monitoring Plans include:

Activity. List all activities that could potentially cause a negative impact to human health or the natural environment.

Mitigation Measure(s). Describe the mitigation measure(s) that will avoid or reduce the negative impact.

Monitoring Indicator(s). Specify the indicators or criteria that will determine if the mitigation measure is in place (being implemented) and its level of effectiveness (visual observation, tests, institutional reports, etc.).

Monitoring and Reporting frequency. Describe how often the mitigation should be monitored and where the findings should be reported.

Parties Responsible. Describe who is responsible for implementing the mitigation measure, who monitors to verify it is being implemented and who is responsible for reporting on the findings. Responsibilities for implementation of mitigation and monitoring measures should be clearly identified, with the agreement of those identified, and updated regularly (at least annually).

The cost and source of funds for mitigation and monitoring should be included in the intervention cost estimates. The mitigation implementation schedule should be seamlessly integrated into the overall malaria disease control activity implementation plan.

The EMMP provides detailed descriptions of how mitigation measures should be planned, implemented, monitored, and evaluated, and what action should be taken when mitigation activities are poorly implemented or fail. SEAs should also include the appropriate elements of the EMMP and include the mitigation measures that are relevant to the malaria control intervention(s) that have been selected for that particular country program.

5.1 MONITORING RECOMMENDATIONS

Several monitoring activities are recommended for the USAID Malaria Vector Control Program: mitigation monitoring, environmental impacts monitoring, entomological monitoring including resistance monitoring and malaria case monitoring. Based on the results of these monitoring activities, adaptive management of intervention implementation and the overall vector control strategy should be a part of every intervention. These activities are discussed in more detail below, and the exact recommended versus required monitoring activities will be spelled out in tiered environmental documents (e.g., SEAs, PERSUAPs, or IEEs).

Mitigation Monitoring. Mitigation monitoring is used to determine if mitigation measures are being implemented and if those measures are effective in preventing or mitigating adverse environmental impacts. During implementation, mitigation monitoring by USAID, independent partner(s), and/or implementing partner(s) should be used to assess the effectiveness of mitigation efforts at defined intervals. Mitigation efforts should be adjusted to address any negative impacts on human health or the environment that are observed.

Table 5-1 contains recommended mitigation recommendations for any insecticide-based vector control activity.

Table 5-1. Recommended Insecticide-Based Vector Control Activity Mitigation Measures

POTENTIAL NEGATIVE ACTIVITIES/IMPACTS	RECOMMENDED MITIGATION ACTIONS
Application of an ineffective insecticide or intervention, lessening the impact on malaria control and/or contributing to insecticide resistance	Entomologic monitoring of insecticide resistance (as the narrative below notes, there may be emergency situations where USAID supports LLINs without associated insecticide resistance testing; the justification for not supporting insecticide resistance should be clearly spelled out in tiered country-specific environmental documents)
	Laboratory testing of insecticide to ensure quality control
	Limiting procurement to products that have been assessed in a MVC PEA or PEA revision and are registered by the host country
	Selection of insecticide that accounts for duration of malaria transmission season
	Selection of intervention that accounts for vector ecology and behavior
	Encourage countries to adopt/support countries in drafting integrated vector control strategies that accounts for epidemiological and entomological parameters
Generation of insecticide stockpiles	Careful quantification of the insecticide to be used to minimize leftover stock from year to year
	If there are insecticide stocks or insecticide-treated products that will expire prior to the next round of use (IRS campaign, net campaign, etc.,), identify options to negate the expiry (e.g., recertify the insecticide, redirect nets to routine distribution channels in gaps between mass campaigns, check to see if another country can utilize the stock, etc.)
Non-conformance to Regulation 216	Development of country-specific environmental documentation (e.g., SEAs, IEEs, PERSUAPs) that fulfills the requirements of Regulations 216 and host country regulations

POTENTIAL NEGATIVE ACTIVITIES/IMPACTS	RECOMMENDED MITIGATION ACTIONS
	When needed, prepare corrective actions and/or revise environmental mitigations in the EMMP to address noncompliance with SEA/IEE.

Environmental and Human Health Impacts Monitoring. Environmental impacts monitoring measures ecological change over time as a result of program interventions. This type of monitoring uses key environmental indicators (e.g., vegetation change, water quality, pesticide levels present in the environment, indicator species populations, depending on the intervention or pesticide used) and baseline surveys to determine the impacts of the interventions on target and non-target environmental areas. Typically, environmental impacts monitoring is only conducted when DDT is used, given its bioaccumulative properties (the 2012 PEA includes the results of USAID-supported environmental impact monitoring for DDT). Additionally, human health effects from pesticide use can be monitored either indirectly, by using patches on the body to measure exposure, or directly, by sampling breast milk, urine or blood (depending on the pesticide). This type of monitoring could be implemented for both those who apply pesticide and community residents. To date, human health impacts monitoring has only been conducted for one of the OP compounds (see Section 5.2 for more information). An environmental monitoring plan for the environment or human health, if needed, should be developed using the following steps:

- Determine the reason for monitoring (e.g., assess the impacts of activity interventions, identify environmental impacts, and monitor mitigation measures)
- Formulate specific questions to be answered by monitoring
- Select indicators
- Determine the monitoring tools required to measure indicators
- Gather and integrate existing data (consider methods of data storage and analysis)
- Identify environmental "hot spots" (location of ecosystems and species at high risk)
- Design a sampling scheme
- Establish baseline conditions and data
- Establish targets for each indicator
- Validate the relationship between indicators and planned results
- Analyze trends and recommend management actions (e.g., environmental mitigation measures) (USAID 1996)

Entomological Monitoring (including Resistance Monitoring). The primary function of entomological monitoring associated with vector control activities is to assure that interventions are effective in controlling the malaria vector. Such monitoring is essential for IRS, LLINs, and larval control. Such monitoring will aid in the identification of insecticide resistance trends and the ensuing selection of appropriate pesticides and resistance management methods. The monitoring program must include the following indicators:

- Species composition and seasonality of malaria vectors in intervention areas, to determine which vectors exist, their abundance, relative proportions, and distribution in intervention areas over time.
- Vector feeding time and location, to determine vector feeding locations (i.e., outdoors versus indoors) and feeding times to understand where and when transmission is occurring.
- Insecticide susceptibility and resistance intensity, to determine vectors' susceptibility to insecticides currently in use or to be used in the future, and to determine the intensity of identified resistance. On occasion, LLINs are deployed in response to emergency situations – to quickly provide protection in the face of other public health emergencies (e.g., Ebola virus disease), to provide protection in the face of malaria epidemics, etc. Because, as described in Section 2, LLINs have been proven effective from an epidemiological perspective in the face of pyrethroid resistance, entomological monitoring activities may not be required. However, going forward, insecticide resistance monitoring has a greater role to play in informing deployment of LLINs given the availability of non-pyrethroid LLINs. Whether insecticide resistance monitoring is required or not will ultimately be decided in tiered environmental documents.

- Mechanisms of resistance, to identify the underlying mechanism of resistance.
- For IRS only: Quality assurance and residual efficacy monitoring, to determine the quality of IRS and the efficacy of the intervention (e.g., to determine how long insecticides last in killing or knocking down vectors).

While not mandatory, residual activity of insecticides on LLINs and physical durability of the netting material can also be monitored for due diligence. PMI has developed standard operating procedures for such testing, available at: https://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/best-practices-indoor-residual-spraying-feb-2015.pdf?sfvrsn=4.

The methodology for collecting and analyzing these indicators is articulated in PMI's Annual Technical Guidance (publicly available at pmi.gov).

Malaria Case Monitoring. Malaria case monitoring is conducted to assess the impacts of malaria control interventions on target human populations. The information obtained from this impact monitoring can be used to determine if the interventions are achieving the desired results and to inform changes in the program. However, care must be taken to ensure that impact of vector control programs consider several confounding factors, such as availability of antimalarials, access to health services, quality of health services, and climate.

5.2 INTERVENTION-SPECIFIC MITIGATION RECOMMENDATIONS/POLICY UPDATES

Indoor Residual Spraying Mitigation Measures

USAID has gained a decade of experience in implementing IRS programs under PMI. The recommended mitigation measures contained in **Annex K** reflect that experience. In addition, this revised PEA takes into consideration the pathways of greatest risk, thereby emphasizing mitigation measures that have the greatest potential for protection of humans and the environment.

As the risk screening results obtained in Section 4 conclude, the potential for noncancer effects for Actellic 300CS suggest that some additional precautions be taken to decrease dermal exposure. Specifically, a toddler's exposure by touching sprayed surfaces is the receptor/pathway of greatest concern, followed by a toddler and infant's exposure via the inhalation pathway. In late 2016/early 2017, PMI will support an operational research study with Actellic 300CS to determine if spraying only the top half of a wall surface is as effective as spraying the whole surface of the wall; results of the operational research study will be used, in part, to refine standing operating procedures, and if spraying the top half only is deemed effective, then this practice will negate toddlers' dermal exposure pathway. In addition, one of the mitigation measures included in Annex K is ensuring that residents do not enter sprayed houses for at least two hours, which will partially reduce inhalation exposures.

Because pesticides have been shown to cross the placental barrier, and their accumulation in break milk can result in elevated exposures for infants, USAID takes additional precautions to protect these sensitive subpopulations. Pregnant women and nursing mothers are prohibited from handling pesticides in the course of IRS work. When recruiting spray operators, pregnancy tests must be conducted during a normal medical exam to ensure that pregnant women are not hired into positions involving any pesticide contact. For spray campaigns lasting longer than 30 days, the pregnancy tests should be repeated once every month during the duration of the campaign. In the event that a pregnancy is discovered on a follow-up test, the woman will be reassigned (and will continue to receive compensation) for the remainder of the campaign to work that does not involve any contact with insecticide.

Indoor Residual Spraying Policy Updates

There are two key policy updates for IRS: biomonitoring for OPs and use of DDT.

Biomonitoring for Organophosphates (OPs): OP compounds owe their insecticidal effect to the

inhibition of cholinesterase (ChE) enzyme activity in the nervous tissue. In humans, cholinesterase is important in several nervous system functions. Acetylcholinesterase (AChE), which is present in tissues of the nervous system and in red blood cells (RBC), performs the breakdown of acetylcholine, the chemical mediator responsible for physiological transmission of nerve impulses at different sites. Plasma cholinesterase (PChE), a group of enzymes present in glial cells, plasma and the liver, can also be inhibited by OPs, although the exact physiological function of PChE is unclear. Acute OP poisoning can lead to symptoms such as excessive sweating, headache, weakness, nausea, and vomiting. Because these symptoms are non-specific, it is often difficult to attribute OP poisoning to them. Cholinesterase biomonitoring in persons working with OPs can help identify exposed workers before they become acutely symptomatic.

Because of OPs' ability to inhibit ChE, and because use of OPs was relatively new (compared to use of pyrethroids and carbamates) to USAID in the context of IRS, one of the mitigation measures in the 2012 MVC PEA was to pilot biomonitoring if USAID-funded programs began utilizing OPs for IRS.

Just after the release of the 2012 MVC PEA, a longer-lasting OP (pirimiphos methyl, Actellic CS) became commercially available and began to be utilized in PMI-supported IRS programs. Therefore, in 2015, USAID supported implementation of a biomonitoring pilot in Ghana. The pilot's two objectives were to (1) evaluate worker OP exposure levels, and (2) determine whether a biomonitoring program was logistically feasible in the contexts in which PMI is supporting IRS. Both AChE and PChE levels were measured using blood samples analyzed by a portable test kit. Baseline testing was undertaken prior to the initiation of the spray campaign, and follow-up testing was conducted at regular intervals throughout the five-week spray season. A pre-determined algorithm was followed that determined the appropriate action based on an individual's weekly results.

Annex N contains the full write up of the biomonitoring pilot, including a detailed methodology and results. A brief summary of results is presented below.

In the algorithm developed to guide decision making based on test results, workers were removed from spray operations for two to three days at a time if either AChE depression of more than 20% but less than 30%, or PChE depression of more than 20% but less than 40%, was present on repeat testing. Workers were removed from operations for approximately five consecutive days if either AChE or PChE depression of more than 40% was present on repeat testing. Workers returned to operations when levels returned to their baseline range.

Exposure Results

There were no clinical symptoms reported among spray personnel. No true AChE depressions were recorded (six participants were thought to have AChE depression, however it was due to inaccurate baseline readings). However, PChE depression was frequently recorded. Throughout the spray season, nearly 50% of workers who participated in the pilot had to be removed from operations at some point during the campaign due to PChE depression. While the number of workers removed from IRS operations was significant, the algorithm determining when to remove workers was highly conservative. For example, by contrast, workers participating in biomonitoring programs in Washington and California are removed when AChE falls 30% or more from baseline or PChE falls 40% or more from baseline. If this algorithm was used instead, only 14 people would have been removed in Week 1 (6%) compared to the 52 people removed in Week 1 (21%) using the Ghana protocol. Due to differences between the protocols, additional comparisons are not able to be made for subsequent weeks.

A majority of participants were retrospectively questioned to collect information on behaviors or characteristics that could explain the high frequency of PChE exposure (e.g., category of employee, use of full PPE, gender, age, etc.). While sample sizes were too small to draw conclusions, approximately half of workers (56 of 113) who noted that they often had to fix their spray pumps during the campaign were removed from operations at some point, and all those who indicated that they always removed their gloves to fix the pump nozzles were at some point removed from operations as a result of PChE depression.

Feasibility Results

Implementation of this pilot biomonitoring program was challenging and labor intensive. The most significant challenges faced included:

- The labor involved in implementing the biomonitoring pilot impacted the project's ability to conduct IRS, as supervisors' attention was diverted to supervising biomonitoring and the number of sprayers removed from operations increased the duration of the spray campaign, which already abuts the rainy season.
- The reagents used in the test kits are sensitive to extreme heat and degrade when the temperature reaches 30 degrees Celsius. Nearly all test kits degraded and accurate baselines were only obtained for 50 participants, thereby requiring baseline retests and the procurement of refrigerators and generators.
- In several instances, the lab technicians could not conduct the tests because they were needed in their regular positions at the health facilities.

Recommendation Results

USAID will not require countries using pirimiphos methyl to routinely conduct biomonitoring for spray personnel. This decision is in alignment with current guidance from the USEPA and the WHO. The USEPA decided not to require routine cholinesterase upon revising (in 2015) the Worker Protection Standard in large part because cholinesterase depression was caused by pesticide handlers not following basic safety and hygiene procedures (e.g., not wearing the required PPE or failing to wash before meals or bathroom breaks)[15]. The 16th WHOPES Working Group Report contained the safety and efficacy results of pirimiphos-methyl (Actellic). The WHO concluded that, "provided that operational guidelines are followed, routine cholinesterase monitoring of spray men during indoor residual spraying programmes is not required." This statement was based on risk modeling that conservatively took into consideration a range of exposure levels.

However, regardless of the rigorous training policy and oversight measures to ensure compliance to PPE, the pilot did demonstrate that workers are being exposed at some level to pirimiphos methyl over the course of their work (which is consistent with studies of agricultural workers in the United States). Therefore, USAID has identified two institutional controls to be strengthened and one area of possible innovation in order to improve the protection of spray personnel:

1) *Strengthen training and supervision surrounding appropriate pump maintenance*. The biomonitoring pilot identified a key area of non-compliance to PMI Best Management Practices: the frequency of spray operators who reported removing their gloves to fix blockages in the pump nozzle, thereby increasing the potential for dermal exposure. USAID will reinforce appropriate pump maintenance by (1) assessing the sufficiency of the current levels of pump mechanics, who are employed in most countries, to determine whether more are needed to repair and maintain spray equipment, and (2) reinforcing oversight of use of PPE to supervisors.

2) *Daily documentation of spray operator's health*. USAID will formalize its current practice of assessing and documenting relevant symptoms of all spray operators prior to their deployment in the field each day by adding specific questions surrounding the health of each spray operator to the morning mobilization checklists. This daily check will be completed by site supervisors and summary reports will be reviewed and monitored by the in-country senior management team on at least a weekly basis. Any spray personnel experiencing symptoms of illness will be referred to a health center, as

[15] The USEPA decided against requiring cholinesterase monitoring for three principal reasons: (1) the revised Worker Protection Standard requires expanded handler training, 2) the recent requirements for revised labeling of Ops, which include increased protections such as requirements for closed systems, and 30 concerns about the high costs and burden. (https://www.epa.gov/pesticide-worker-safety/agricultural-worker-protection-standard-wps)

appropriate, and will continue to receive wages in order to remove barriers to reporting illness. Formalizing this reporting system will ensure that any cases of insecticide-related illness are detected early and responded to in a timely manner. USAID will continue to ensure that clinicians are trained on insecticide poisoning and that the necessary drugs to treat such cases of poisoning are supplied at health facilities within IRS catchment areas, as appropriate.

3) *Additional research on ways to improve personal protective equipment (PPE).* USAID will explore potential innovations in PPE design, given cloth coveralls easily absorbs sweat, and therefore, increases potential for dermal exposure to insecticides.

If there is an incident or concerns – such as documented insecticide poisoning of an IRS worker or widespread non-compliance with PPE requirements by spray personnel – that indicate that routine operational guidance is not being followed, then USAID and its implementing partners will follow established protocols for adverse incident or non-compliance reporting. While this protocol is developed between the COR/AOR and the partner, and therefore may be different based on mechanism, the process is generally as follows:

- Project leadership immediately notifies the Contracting Officer's Representative (COR)/Agreement Officer's Representative (AOR) and Mission.
- A written incident report is submitted to the COR/AOR and Mission within 48 hours of the incident occurring.
- The COR/AOR will notify relevant Environmental Officers and HQ or Mission Leadership. The COR/AOR, Environmental Officers, and any other relevant USAID staff will then assess root causes and propose a corrective action plan. Part of the corrective action plan *may* entail conducting cholinesterase biomonitoring during the next spray round.

The policy to not conduct routine biomonitoring for pirimiphos methyl, but to consider conducting biomonitoring as part of a corrective action plan, does not apply to other OPs. If USAID employs other OPs (e.g., malathion or fenitrothion), then USAID will discuss the necessity of biomonitoring and will continue to look to WHO guidance on the necessity of biomonitoring.

Use of DDT: In select countries, USAID, under the PMI, has supported IRS with DDT since 2006. Precise mitigation measures – including those that incorporated principles of the Stockholm and Basel Conventions – were developed and followed. In addition, USAID supported environmental impact monitoring in Mozambique and Zambia; results were included in the 2012 PEA.

DDT is an insecticide listed as a persistent organic pollutant under the Stockholm Convention. Under the Stockholm Convention, the DDT Expert Group was established in consultation with the WHO to assess, every two years, the available scientific, technical, environmental, and economic information related to production and use of DDT. The latest meeting of the Conference of Parties concluded that "countries that are relying on DDT for disease vector control may need to continue such until locally safe, effective, affordable, and environmentally sound alternatives are available for a sustainable transition away from DDT". The specific decision coming from the latest meeting was that the Conference of the Parties:

1. *Adopts* the format of the DDT register contained in Annex I of the present decision and requests the Secretariat to continue to make it publicly available on the Convention website (www.pops.int);

2. *Approves* the form for notification of production and use of DDT for disease vector control contained in Annex II of the present decision and requests the Secretariat to continue to make it publicly available on the Convention website;

3. *Reminds* Parties of their obligation in paragraphs 2 and 3 of part II of Annex B to the Convention to notify the Secretariat of their intention to produce and/or use DDT for disease vector control, and to do so by means of the form referred to in paragraph 2 above;

4. *Adopts* the format and questionnaire contained in Annex III to the present decision and requests the Secretariat, in cooperation with the WHO, to keep under regular review the adequacy of the information required under sections A, B, C and D thereof and propose to the Conference of the Parties any modifications that are deemed essential;

5. *Reminds* Parties that use DDT for disease vector control to provide to the Secretariat and the WHO (in 2007 and every third year thereafter) information on the amount used, the conditions of such use and its relevance to each Party's disease management strategy, as required under paragraph 4 of part II of Annex B to the Convention;

6. *Reminds* Parties that produce, use, export, import or maintain stocks of DDT to so inform the Secretariat and the WHO through sections A, B, C and D of the questionnaire set out in Annex III to the present decision in order to assist the Conference of the Parties in its evaluation of the continued need for DDT in disease vector control;

7. *Adopts* the list of information items needed for the evaluation of the continued need for DDT for disease vector control set out in Annex IV to the present decision and requests the Secretariat, in cooperation with the WHO, to keep under regular review the adequacy of the information required and propose to the Conference of the Parties any modifications that are deemed essential;

8. *Takes note* of the report of the expert group contained in annex II to the note by the Secretariat on evaluation of the continued need for DDT for disease vector control, including the conclusions and recommendations contained therein, and based on them:

    (a) *Concludes* that countries that are currently using DDT for disease vector control may need to continue such use until locally appropriate and cost-effective alternatives are available for sustainable transition away from DDT;

    (b) *Concludes* that sufficient capacity at the national and subnational levels is necessary for effective implementation, monitoring and impact evaluation (including associated data management) of the use of DDT and its alternatives in disease vector control, and recommends that the financial mechanism of the Convention support activities to build and strengthen such capacity as well as measures to strengthen relevant public health systems;

    (c) *Requests* the Secretariat, in cooperation with the WHO, to elaborate further the reporting and evaluation process on DDT, as envisaged in the first recommendation of the expert group report on DDT, and to prepare cost estimates on such a process for consideration by the Conference of the Parties at its second meeting;

    (d) *Requests* the Secretariat, in cooperation with the WHO, to provide an overview of alternatives and their effectiveness to assist Parties in their goal of reducing and ultimately eliminating the use of DDT;

    (e) *Decides* that adequate resources should be budgeted for 2006 to meet the needs specified for activities 2 and 3 of the work plan outlined in Annex III to the note by the Secretariat on evaluation of the continued need for DDT for disease vector control, on immediate actions to support the preparations of Parties for reporting on DDT and the review and assessment process required for future evaluations of the continued need for DDT, and invites countries to provide in 2005 the resources necessary for activity 1;

(f) *Requests* the financial mechanism of the Convention, and invites other international financial institutions, to support ongoing processes to develop global partnerships on long-term strategies for developing and deploying cost-effective alternatives to DDT, including the development of insecticides for indoor residual spraying, long-lasting insecticide treated materials and non-chemical alternatives;

(g) *Requests* the Secretariat to work closely with the WHO on ongoing efforts to provide global leadership for the partnerships referred to in subparagraph 8 (f) above;

9. *Invites* States that are non-Parties to the Convention to participate in the activities outlined above.

USAID has not supported IRS with DDT since 2012 for two primary reasons: (1) widespread insecticide resistance to DDT, and (2) limited-to-no supply of quality-assured DDT. However, the United States Government, as a signatory to the Conference of the Parties to the Stockholm Convention on Persistent Organic Pollutants, supports the most recent Conference Meeting decision on DDT. USAID will therefore support the use of DDT where there is an approved SEA in place and when there are no safe, effective, and affordable alternatives, and will ensure that appropriate safeguards are in place to prevent leakage into the agricultural sector and unsafe disposal of unused DDT and DDT-contaminated materials exist. To ensure that DDT is only used under these circumstances, USAID requires annual supplementary environmental assessments for countries using DDT for IRS. In addition, because of DDT's bioaccumulative properties, USAID prohibits utilization of women as spray operators in countries using DDT (instead, they can be directed to positions such as community mobilizers). Finally, USAID will continue to support research and development for new insecticides to expand the arsenal of insecticides which can be used, thereby decreasing reliance on DDT even more.

LLIN Mitigation Measures

USAID has gained more than a decade in implementing LLIN programs under PMI and the Office of Foreign Disaster Assistance. The recommended mitigation measures in **Annex L** reflect that experience.

LLIN Policy Updates

Since the updating of the previous PEA (in 2012), USAID and the global malaria community at large have collaborated and supported studies to better understand the potential impact of misuse, repurposing, and disposal/end-of-life (EOL) issues associated with nets. Efforts have included (but are not limited to): a multi-part study to identify and assess the feasibility of environmentally sound and cost effective options for collection, recycling, and disposal of LLINs in Kenya and Tanzania (jointly funded by Canada POPs Trust and the World Bank) and a complementary pilot in Madagascar (funded by the UNEP Strategic Approach to International Chemicals Management); an inception meeting to frame the pilot projects' scopes at the WHO Headquarters in 2010; meetings/discussion over the course two years from a temporary WHO World Group on the sustainable life cycle management of LLINs (of which USAID participated); and PMI-supported pilot projects to assess the feasibility of recycling used nets and net packaging.

The framework for these projects and discussion are generalized below:

- Good stewardship should include consideration of end-of-life care for LLINs.
- LLINs are being re-used in and around the household, and these uses are of genuine value to extremely poor populations.
- Most repurposing activities pose minimal to no health or environmental risks.

- The proportion of the total LLIN plastic waste in target communities is small compared to overall plastic waste.
- Country specific contexts are important and must be considered, as is community/individuals perceptions.
- Maintenance of LLIN coverage and usage is critical.

Misuse

Misuse is defined as the use of a viable LLIN for purposes other than its intended use as a bed net to protect against malaria infection. Misuse of LLINs is not acceptable under any circumstances and not only defeats the public health purpose of providing protection from malaria, but can also have negative environmental outcomes. The most ecologically damaging use of LLINs is likely fishing, given pyrethroids are toxic to aquatic organisms, not particularly soluble in water, and have a high affinity for organic matter. Pyrethroids can kill fish, especially young fish, aquatic crustaceans, and insects when leached from a viable LLIN being used for fishing. Mosquito nets have a very small mesh size, are non-selective, and may be dragged through littoral habitats, which form important nursery and breeding areas for a number of fish species. This is less of an issue in larger bodies of water but can be a significant problem in small streams and ponds. There are no other known misuses of viable LLINs that pose serious environmental risks. However, Ng *et al.* describe the substantial uncertainty when trying to model environmental risks associated with non-fishing misuse (uncertainty that arises from trying to identify distribution and degradation rates). They conclude that there isn't enough data available to predict with certainty the risk to media outside water, such as emissions to soil, crops, and vegetation.

It is critical to note that what remains unclear among the global community is– despite the risks (albeit highly variable) to aquatic environments – whether these risks translate into a problem. More data, particularly on the extent of misuse for fishing, is needed to answer the "is it a problem" question. Although reports in the media have claimed that LLINs are frequently and widely misused for fishing, these claims have been dispute. Specifically, there is "very little evidence to support claims of widespread misuse across Africa[16]." In 2015, to better understand the extent of misuse of bed nets for fishing and the associated risks, USAID commissioned an analysis to identify the risks and characterize the circumstances under which the use of LLINs for fishing would be detrimental to fish populations in sub-Saharan Africa using a comprehensive literature review and questionnaire-based survey.[17]

The analysis identified the following as drivers of misuse of nets for fishing: income status of fishers, as low-income fishers were unable to afford alternative fishing gears; gender, as women and children are by far the greatest users of mosquito net fishing gear; and overfishing, as a response to declining catches.[18] Misuse for fishing appears to be increasing most likely due to the frequency with which LLINs are being replaced and the use of old/used nets for fishing.

The analysis also included a fisheries risk assessment. However, because of the poor quality or lack of quantitative and qualitative data (particularly on catch and effort, size, and species composition), the authors relied on a lower-level qualitative risk assessment modified from the consequence-likelihood approach in

16 Eisele TP, Thwing J, Keating J. Claims about the Misuse of Insecticide-Treated Mosquito Nets: Are These Evidenced Based? 2011, Plos Med 8(4): E1001019.DOI:10.1371/journal.pmed.1001019.

Koenker, H, et al, "What happens to lost nets: a multi-country analysis of reasons for LLIN attrition using 14 household surveys in four countries" 2014, Malaria Journal 13(464) DOI: 10.1186/1475-2875-13-464

17 The analysis is currently undergoing final review by USAID. Upon approval, it will be publically available at pmi.gov.

18 Impact of mosquito net fishing gears on fish populations in sub-Saharan Africa, Dec 21, 2015, VectorWorks

Fletcher[19] and the resilience/fishery impact index in Astles *et al.*[20] Risks posed by mosquito net fishing were identified, analyzed, and evaluated for different environments and for fish species/species groups. The analysis demonstrate that environments at high risk from seining by mosquito nets include sandy beaches, mangroves, sea grass beds, coral reefs, and the littoral zone of lakes because they are prone to physical damage from seining and act as important nursery and/or spawning areas. Floodplain environments are highly resilient and demonstrate high biological turnover. The analysis also noted that species that are characterized by rapid growth, early age-at-maturity, high fecundity, and high natural mortality were more resilient to the impacts of mosquito net fishing.

Because of results from the analysis and because of the increasing frequency of reports indicating that nets (whether new or used/expired) are being misused for fishing, USAID is working to develop an assessment that countries can utilize to assess the extent of misuse. This tool was recently piloted in Malawi and is being refined. Responding to the problem is challenging and multi-sectoral, involving Ministries of Health, Environment, and Fisheries. Many countries have existing regulations or laws that forbid use of mosquito nets for fishing, but oversight of these regulations are lax or there isn't sufficient capacity. USAID has incorporated mitigation measures against misuse for fishing (see **Annex L).**

Repurposing

Repurposing is defined as the use of expired, non-viable LLINs for purposes other than as a bed net to protect against malaria infection. It is very clear that repurposing of nets for non-malaria uses is a common practice, and there is a wide range of use with the most common observed outdoor uses for visual/physical barriers (privacy screens, crop protection from insects and birds, or fencing for animals). Observed indoor uses were more varied and include conversion of EOL nets to clothes lines, seat covers, ropes, screens for windows, burial shrouds, wedding dresses, and mattress stuffing.

While old nets have lower doses of insecticide, a leachate study that was commissioned as part of the Canada POPs Trust/World Bank study found that, even after 3-5 years of use, there were measurable residues leaching out of nets with large variability in the data (from non-detectable limit concentrations to significant concentrations (up to 83% of original insecticide content)). It should be noted that the leachate study only sampled from two types of nets, with small sample sizes within those two net types. Despite the presence of insecticide on EOL nets, there is unclear evidence that repurposing – besides fishing – poses environmental hazards.

Disposal of LLINs

The Canada POPs Trust/World Bank study focused most intensely on the issues of disposal of LLINs and, to a lesser extent, LLIN packaging. First and foremost, UNEP determined that nets and their packaging were not considered hazardous waste under the Basel Convention. The study was originally going to pilot recycling efforts in Tanzania and Kenya. However, at an inception meeting prior to the launch of country activities/surveys, there was strong concern that there were social, ethical, and community aspects that might impact any attempts to collect, recycle, or dispose of LLINs. Those concerns, coupled with a limited study timeframe, precluded any pilot recycling/take back programs.

Instead, surveys were conducted to identify under what conditions individuals/communities would return used/EOL LLINs. Informants in all interviews in Kenya reported that nets, once issued to families, were household property and could only be collected with an agreeable arrangement with owners (e.g., replacement with a new net or cash back). In Tanzania, although community members were more willing to give up nets, they preferred an incentives system (most commonly identified as trading an old net for a new net). Burning

19 Fletcher, W.J. 2005. The application of qualitative risk assessment methodology to prioritize issues for fisheries management. ICES Journal of Marine Science, 62(8), 1576-1587.

20 Astles et al. A qualitative risk-based assessment of impacts on marine habitats and harvested species for a data-deficient wild capture fishery. Biological Conservation, 142, 2579-2773.

of EOL nets – after they have been repurposed for years – is a common practice, and communities did not perceive nets as contributing to general waste.

While an actual recycling pilot was not conducted, the study did explore the logistical feasibility (pending individuals would part with nets) of a recycling program. The study was contradictory in assessing the feasibility, as it noted that consultants were not able to identify a single recycler in the countries (Tanzania, Kenya, and Madagascar) with the capacity to safely recycle LLIN materials without significant upgrades or technical assistance, while later noting "experience proves that the recycling option is more than feasible". The logistics of collection were also explored. Many community members expressed a preference for door-to-door collection of nets, which raised questions of cost and feasibility.

The report noted the opportunity to work with UNFAO and CropLife International to develop pilot national EOL recyclers or energy recovery facilities suitable for pesticide tainted plastics.

Until more definitive information is available, the report concluded by advising NMCPs to weigh "each known and probable benefit against each known and probable liability, including potential impacts on LLIN coverage/usage, financial costs, availability of suitable final dispositions and environmental footprint or health risks associated with conducting a LLIN related recovery programme or not".

The only known implementation of a net recycling program was supported by USAID (under PMI) in 2010 in Madagascar.[21] The program looked at several key factors including recovery, transporting, and parameters for converting expired LLINs into a viable alternative product. It was determined that the technology required for this process was not available in Madagascar, and therefore used LLINs were shipped back to the United States for processing. Overall, the cost of implementing a take-back program was prohibitively high. The total collection cost per net was $5.44 when accounting for both the cost of the activity and the partner's management/oversight responsibility. Even when subtracting the partner's management/oversight responsibility, the cost was $2.72 a net, which is nearly double the cost of distributing a net and slightly less than procuring an LLIN at the time of the pilot. In addition, many residents were reluctant to give up nets, no matter how old.

Findings from the report and its associated studies, along with other background information (including results from the PMI-supported pilot recycling efforts), were presented to the Technical Expert Group on Malaria Vector Control in March 2014 for review. The WHO Technical Expert Group indicated that the material presented was sufficient to form global recommendations on best practices in relation to managing LLIN waste as follows:

- Residents should be advised to continue using nets until they have a new LLIN to replace it.
- Residents should be advised not to dispose of LLINs in any water body, or use LLINs for fishing.
- NMCPs should only collect LLINs if the communities are covered, and if there is a suitable plan for safe disposal of the collected LLINs (the report found that recycling and incineration were not practical or cost-effective in most settings, confirming the results from PMI's recycling pilot).
- Collecting old LLINs should not divert effort from core duties, including maintaining universal coverage.
- If LLINs and packaging are collected, the best option is high-temperature incineration, not burning in open air. If this is not possible, the next best option is burial, away from water sources.

21 Nelson, Michelle, Ralph Rack, Chris Warren, Gilles Rebour, Zachary Clarke, and Avotiana Rakotomanga. 2011. LLIN Recycling Pilot project, Report on Phase II in Madagascar. Arlington, Va.: USAID | DELIVER PROJECT, Task Order 3. AND Nelson, Michelle, and Ralph Rack. 2012. Madagascar: LLIN Recycling Pilot Project, Report on Phase III. Arlington, Va.: USAID | DELIVER PROJECT, Task Order 7. Both reports can be downloaded at: http://deliver.jsi.com/dhome/search?p_search_tok=madagascar+recycling&btnG=search

- NMCPs should work with national environment authorities to take WHO recommendations into consideration when formulating local guidance.

  The WHO recommendations are captured in Annex L. In addition, in light of the lack of appropriate/feasible EOL options and uncertainty that EOL LLINs present environmental risks, USAID will continue to work with recipient countries and other donors (e.g., the Global Fund) to monitor and report any disposal issues that arise. Finally, USAID is supporting communication messaging about the dos and don'ts of EOL use of LLINs. The messaging is not meant to instruct residents when to stop using nets, but rather to include messaging on specific, neutral EOL options such as covering gardens/plants/small trees, concealing latrines, covering chicken coops, and molding into sports gear (e.g., soccer balls, goals, etc.).

Disposal of LLIN Packaging

Nets can be packaged in two ways. Most commonly, nets are individually wrapped in plastic bags which are then packaged together in bales of (typically) 40 or 50 nets. Nets may also be procured without individual wrappers (known colloquially as bulk packaging or 'naked' nets) which are then bundled together with an outer plastic wrapper into bales (again, in units of 40 or 50 nets per bale). There are clear programmatic advantages to each type of packaging option, depending on how the bed net is to be distributed. Countries have begun to request bulk packaging for mass distribution campaigns when individual packaging is typically discarded in mass quantities and can create a significant waste management plan. Individual wrappers on nets serve an important protective role for nets that are distributed periodically through routine distribution channels such as antenatal care clinics, immunization clinics, or schools.

In 2013, after a mass distribution campaign distributed more than 12 million bed nets throughout Ghana, campaign organizers were left with a large amount of residual materials that could create environmental risks. During the campaign, empty plastic bags were collected at designated locations in each district for purposes of accountability and validation of LLINs distributed. The NMCP, assisted by partners, transported over 12 million empty LLIN bags—enough to fill 12.5 40ft containers—from various storage points in the districts to a recycling plant in Ghana where the waste was recycled into pavement blocks that will be used to improve public and private spaces. While the LLIN waste was successfully recycled in Ghana, it was expensive and created significant logistical challenges to collect, store and transport the large volume of waste. A critical lesson learned from this activity was how important it is to include waste management activities from the onset of planning for the mass campaigns.[22]

The Canada POPs Trust/World Bank study included a laboratory-based assessment of pyrethroid residue in individual LLIN packaging. Data initially demonstrated that only a small fraction of insecticide was transferred from the nets to the packaging materials. However, when the study parameters were changed to reflect extreme conditions (e.g., temperatures of 130° F), the residue levels increased 20 times. The report called for donors and manufacturers to explore how to eliminate or minimize packaging that absorbs insecticides. While it is unclear if this extreme situation is realistic or common, because LLIN packaging may be repurposed (e.g., book bags for school, household storage), in 2011 the WHO Global Malaria Programme issued *Recommendations on the Sound Management of Packaging for LLINs*. The detailed recommendations are summarized below (for a complete review, please read the recommendations in full at: http://www.who.int/malaria/publications/atoz/recommendations_management_llin_packaging_nov11.pdf)

22 http://deliver.jsi.com/dlvr_content/resources/allpubs/logisticsbriefs/GH_RecyTurnEnvi.pdf.

Do Not—

- encourage the re-use of LLIN bags for any other purpose;
- burn LLIN bags and baling material in the open air;
- dispose of LLIN packaging as ordinary waste or in improper sanitary landfills.

Do—

- distribute LLINs without leaving any packaging with the intended LLIN user if/where possible and with no reduction in the public health benefit;
- ensure that workers use proper PPE during all stages of operations for collecting, sorting, recycling, and disposing of LLIN packaging;
- incinerate LLIN bags and baling material only if specified high-temperature incineration conditions for pesticide-tainted plastic can be guaranteed; and if UNFAO/WHO and Basel Convention guidelines, as well as national regulations and requirements, can be strictly followed;
- store used LLIN packaging to be recycled or disposed of in dry, ventilated, and secure facilities;
- consider recycling LLIN packaging, if/where possible and only for appropriate products which have limited potential for human contact;
- dispose of LLIN packaging away from any residences, in a landfill that will not leach contaminants, if the manufacturer does not recommend recycling or incineration (or if appropriate disposal methods are not available).

The mitigation measures in the programmatic EMMP for LLINs have been updated to reflect the WHO recommendations for LLIN packaging.

Larvicidal Agent Mitigation Measures

Unlike IRS and LLINs, for which program implementation and therefore mitigation measures are relatively uniform regardless of insecticide product chosen, program implementation and therefore mitigation measures for larviciding are not as standardized – for example, use of PPE ranges from gloves only to respirators and gloves, and application of larvicides ranges from dispersion by hand to spraying by backpack or other small-scale spraying equipment.

Therefore, the recommended mitigation measures presented in **Annex M** are more general than those presented in **Annexes K and L**. Partners preparing EMMPs for larviciding should refer to USAID's Initial Environmental Examination Amendment: Global Health Zika Vector Control Programmatic PERSUAP, which provides more detailed mitigation measures for Bs, Bti, methoprene, monomolecular films, pyriproxyfen, spinosad, and temephos (the Zika Vector Control PERSUAP assessed USEPA-approved larvicides only). Included in the Global Health Zika Vector Control Programmatic PERSUAP is the requirement that, because all product registrations for temephos were cancelled by the USEPA, existing wholesale and retail stocks could be sold until Dec 31, 2016; if purchased by that date, supplies can be used until exhausted as long as uses are consistent with product labelling. No new stocks of temephos can therefore be procured going forward.

5.3 TRAINING AND CAPACITY

5.3.1 INSTITUTIONAL CAPACITY BUILDING

Regulation 216, Pesticide Procedures §216.3(b) states that, "factors to be considered in such an evaluation shall include the provision made for training of users and applicators". The UNDP defines capacity building

as a long-term continual process of development that involves all stakeholders; including ministries, local authorities, non-governmental organization, professionals, community member, academics and more. The goal of capacity building is to tackle problems related to policy and methods of development, while considering the potential, limits and needs of the people of the country concerned.

Training and capacity building are essential components of efforts to assist the host country in developing a sustainable malaria vector control program that ensures the protection of human health and the environment. Different types of training and capacity building are necessary, ranging from in-field training of those who apply pesticides, to local-level management capacity building, to ministry decision making guidance, to helping foster linkages among Ministries of the Environment, Agriculture, and Health.

5.3.2 TRAINING OF CONTRACTORS

USAID Mission Environmental Officers (MEOs) and Mission Health Officers should provide training to contractor program managers and other partners involved in USAID-supported malaria vector control interventions. This training should inform program managers of the importance and methods of integrating human health and environmental concerns into malaria vector control. It should also inform program managers of USAID's expectations for implementation of best practices for human health and the environment as detailed in this PEA and the SEA. Finally, the training should express USAID's expectations of what measures are needed to protect human health and the environment be factored into program evaluation. Additional topics for discussion may include

- Factors to consider in intervention selection
- Factors to consider in pesticide selection
- Potential impacts of pesticides
- Best practices and mitigation measures (throughout the life cycle of the intervention or pesticide)
- Adaptive management

5.3.3 CAPACITY BUILDING FOR CENTRAL-LEVEL OFFICIALS

Capacity building at an institutional level should involve aiding pre-existing institutions. One of the most fundamental ideas associated with capacity building is the idea of building the capacities of governments in developing countries so they are able to handle the problems associated with environmental, economic and social transformation. Developing a government's capacity, whether at the local, regional or national level, will allow for better governance that can lead to sustainable development and democracy.

The Ministry of Health (MOH), including the National Malaria Control Program (NMCP), is made up of experts in a variety of fields. It is not always guaranteed that these government staff will have the knowledge and training on all aspects of malaria vector control, or that decision-making on malaria vector control within the MOH takes into account all appropriate facets of the issues.

As a way of supporting sound decision making on malaria vector control across the globe, and as part of country-specific intervention support, USAID should support training for MOH malaria control program managers and other relevant staff to orient them to the elements of well-run IVM malaria programs, including environmental mitigation and monitoring. Other factors in the training should include the following:

- Factors to consider in intervention selection
- Factors to consider in pesticide selection
- Potential impacts of pesticides
- Best practices and mitigation measures (throughout the life cycle of the intervention or pesticide)
- Appropriate timing and logistics
- Adaptive management

Additionally, contractor specialists should be paired with counterparts from the MOH malaria control program to provide any on-the-job guidance necessary.

5.3.4 CAPACITY BUILDING FOR REGIONAL/LOCAL LEVEL OFFICIALS

Although health systems in the developing world have decentralized and placed responsibility for malaria program implementation on local and regional managers, the management skills necessary for these local and regional managers to perform effectively have not always filtered down from the central ministry. The result is often a lack of capacity to manage malaria vector control programs at the local and regional level.

As part of capacity building efforts contractor specialists should be paired with local and/or regional counterparts to provide on-the-job guidance, training, and practice. Contractor specialists, as necessary, should train mid-level management in

- Logistics
- Data management
- Best practices and mitigation measures
- Monitoring and evaluation (of all types mentioned in this PEA)
- Surveillance systems
- Adaptive management

Additionally, knowledge sharing between central ministry staff and local or regional managers should be facilitated.

5.3.5 CAPACITY BUILDING FOR IMPLEMENTERS

Every malaria vector control intervention requires staff that implements the vector control activities. Each of these implementers should be trained according to the highest standards available based on WHO guidelines, PEA guidelines, UNFAO guidelines, equipment manufacturer guidelines, pesticide industry guidelines, and ministry guidelines. In situations where the interventions are seasonal, refresher training prior to each intervention may be necessary.

Training of users and applicators

To mitigate adverse impacts from the implementation of the interventions, all individuals who handle pesticides or inadvertently come in contact with pesticides, such as storekeepers, spray operators, washpersons, individuals transporting pesticides, as well as medical practitioners and communities, should be educated on their roles and responsibilities in preventing unwanted exposure to pesticides (or treatment of pesticide exposure, in the case of medical practitioners). Supervisors and team leaders should participate in a "Training of Trainers" course. The purpose of "cascade training" is to pass knowledge and skill to colleagues who work at different "levels." In order to teach a trainer how to train well, a "learning by doing" approach is best.[23] The training should be conducted in accordance with standardized training and operations manuals. Essential components of this training are provided in Section 6 of this PEA, Environmental Mitigation and Monitoring.

5.3.6 CAPACITY BUILDING OUTSIDE THE MALARIA SECTOR

Malaria vector control activities interact with other sectors, most importantly agriculture and environment. To the extent that a host-country institution expresses willingness to become involved in environmental monitoring of malaria vector control interventions, promote responsible pesticide use, and prevent pesticide pilferage, USAID-supported interventions should include measures to build the capacity of those institutions and facilitate collaboration between those institutions and the malaria control program.

[23] IMPEC Guidelines for Training of Trainers, September 2002

6.0 REGULATORY, LEGAL, AND INSTITUTIONAL SETTING

6.1 THE NATIONAL SETTING

Partnerships are at the heart of PMI's strategy and operational plans. PMI has forged strong partnerships with host country government in all PMI focus countries, and works closely with other agencies and organizations.

The overarching regulatory framework for conducting environmental assessments for USAID funded projects is 22 CFR 216 (see ***Annex I***); however, host-country environmental policies, laws, and regulations must also be consulted and considered in preparing SEAs and other required approval documents. Support for interventions must abide by host-country environmental regulations, as well as USAID regulations.

Long-term sustainability of any economic or social development project requires that the development interventions be well conceived and that a regulatory framework with enforcement capacity exists.

Public participation in the host country is paramount for successful, sustainable, programs. Host-country government ministries involved in malaria control, pesticide use, or other relevant issues, as well as civil society, should participate in the SEA processes from the onset. Not only do these entities possess the information needed to complete the assessment, but involving them also helps guide the selection of alternative approaches and ensures greater local ownership of the program from the start. **Table 6-1** lists the key host-country institutions that should be consulted.

TABLE 6-1 HOST-COUNTRY INSTITUTIONS WITH MALARIA CONTROL MANDATES OR RELATED FUNCTIONS

INSTITUTION	INFORMATION AND DATA
Ministry of Health	Documents pertaining to malaria control policies, history of control in the country Insecticides registered for use against mosquitoes, pesticide use policies, all donor programs active in the country Maps of vectors and malaria distribution, information about insecticide resistance, pesticide testing procedures, inventories of pesticides and equipment available Organization and malaria control responsibilities in the ministry Measures for treating pesticide poisoning
Ministry of Environment	Potential institution for environmental monitoring Documents and maps pertaining to the presence of sensitive habitats, such as world heritage sites, national parks and forests, lists of endangered species and their locations, game parks, bodies of water, and other environmental resources
Ministry of Agriculture	Pesticide registration Listing of agricultural development programs currently using pesticides, and information on classes of pesticides used in various agricultural activities and locations, ways to prevent public health pesticides from being used for agriculture Potential agricultural export impacts isolated to use of various pesticides
Ministry of Public Works	May be knowledgeable about sanitation laws, regulations, guidelines, and implementation May also work with the MOH in administering routine campaigns to clean up potential malaria mosquito breeding containers or locations
Regional and local governments	Likely to be responsible for implementing some antimalaria campaign activities; information will need to be collected on how and when this is done Measures of program impact

INSTITUTION	INFORMATION AND DATA
Universities	Potential institutions for environmental monitoring Research studies and data pertaining to malaria control programs, toxicity assays, experimental approaches
Environmental nongovernmental organizations	Potential institutions for environmental monitoring Information and maps pertaining to the presence of sensitive habitats, such as world heritage sites, national parks and forests, lists of endangered species and their locations, game parks, bodies of water, and other environmental resources
Affected citizens	Recommendations and concerns to be taken into account in deciding upon, planning, and implementing an intervention

6.2 THE INTERNATIONAL SETTING

6.2.1 INTERNATIONAL TREATIES

International transport and use of pesticides are governed by three major international treaties:

- The **Basel Convention** on the Control of Transboundary Movements of Hazardous Wastes and their Disposal
- The **Rotterdam Convention** on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade
- The **Stockholm Convention** on Persistent Organic Pollutants

The Basel Convention addresses the transboundary movement, management, and disposal of hazardous wastes, including waste pesticides. Transboundary movements of hazardous waste between Parties can take place only on prior written notification by the exporting state to importing (or transit) states, and the inclusion of movement documents with each shipment. In addition, Parties may not permit hazardous wastes to be exported to or imported from a non-Party except pursuant to an agreement or arrangement that stipulates provisions no less environmentally sound than those provided for by the Basel Convention. Finally, trade in hazardous waste cannot take place under conditions in which such wastes cannot be handled in an environmentally sound manner. Parties are obligated to consider illegal traffic in hazardous wastes as criminal and to notify other Party states upon prohibition of import of hazardous wastes for disposal. Export of waste pesticides may require specific compliance activities by the host-country government.

The Rotterdam Convention addresses the transboundary movement of 22 chemicals, including DDT. Parties to the Convention must make decisions on each chemical regarding its import, abide by export limitations delineated in the treaty, and notify Parties receiving exported waste according to treaty conditions. Host-country governments are responsible for complying with any import or export treaty conditions applicable to their status as a Party or non-Party. Import or export of the 22 chemicals covered by the Rotterdam Convention, including DDT, may require specific compliance activities by the host-country government.

The Stockholm Convention addresses the production, import, and export of 12 persistent organic pollutant, including DDT. Currently, Parties to the Convention must take measures to eliminate releases of each chemical, with the exception of certain uses listed in the Convention (for example, the exception of DDT use for "disease vector control"). Parties to the Convention must also abide by the Convention's stockpile handling, transport, and disposal requirements intended to eliminate persistent byproducts. Thus, management and export of obsolete pesticides may require specific compliance activities by the host-country government (see discussion on Stockholm DDT requirement in IRS mitigation section).

6.2.2 INTERNATIONAL INSTITUTIONS

Several international and regional organizations fund and implement malaria control initiatives. Coordination and collaboration is essential so as not to duplicate efforts and resources. When writing SEAs, the activities of each of these groups in the country of interest should be researched and catalogued, and recommendations

for coordination should be included in the report. **Table 6-2** provides an illustrative list of the organizations and programs that may be funding or implementing malaria control or pesticide management activities in specific countries.

TABLE 6-2 ILLUSTRATIVE LIST OF ORGANIZATIONS AND PROGRAMS

INSTITUTION	PROGRAM
RBM Partnership	The RBM Partnership is the global framework to implement coordinated action against malaria. The RBM Partnership was launched in 1998 by WHO, UNICEF, UNDP and the World Bank, in an effort to provide a coordinated global response to the disease. It mobilizes for action and resources and forges consensus among partners. The Partnership is comprised of more than 500 partners, including malaria endemic countries, their bilateral and multilateral development partners, the private sector, nongovernmental and community-based organizations, foundations, and research and academic institutions. RBM's strength lies in its ability to form effective partnerships both globally and nationally. Partners work together to scale up malaria-control efforts at country level, coordinating their activities to avoid duplication and fragmentation, and to ensure optimal use of resources. RBM's overall strategy aims to reduce malaria morbidity and mortality by reaching universal coverage and strengthening health systems.
WHO GMP	WHO Global Malaria Programme (GMP), as part of the World Health Organization, convenes experts to review evidence and set global policies. GMP's policy advice provides the benchmark for national malaria programmes and multilateral funding agencies. GMP's unique position uniting high levels of expertise—and WHO's field presence in all regions and all malaria-endemic countries of the world—ensures harmonized policy advice and the critical technical assistance necessary to effect concrete and sustainable successes at global level. GMP's activities are focused on providing an integrated solution to the various epidemiological and operational challenges. This is done by promoting sound, evidence-based and locally appropriate strategies. The Programme helps countries reach the most vulnerable populations and ensure that needed interventions take into account social, economic and environmental realities.
UNEP GEF projects	The United Nations Environment Program Global Environment Facility helps developing countries fund projects and programs that protect the global environment. The Global Environment Facility's grants support projects related to biodiversity, climate change, international waters, land degradation, the ozone layer, and persistent organic pollutants (POPs)—a new focal area, as they are a threat to biodiversity and even have the potential to cause disruption at the ecosystem level.
WHOPES	The WHO Pesticide Evaluation Scheme, set up in 1960, is the only international program that promotes and coordinates the testing and evaluation of new pesticides proposed for public health use. It functions through the participation of representatives of governments, the pesticide industry, WHO Collaborating Centers and university associations, associate laboratories, as well as other WHO Programs, particularly the International Program on Chemical Safety. WHOPES facilitates the search for alternative pesticides and application methodologies that are safe and cost-effective and helps develop and promote policies, strategies, and guidelines for the use of pesticides in public health, and ultimately, helps monitor their implementation by the Member States.

INSTITUTION	PROGRAM
Global Fund for AIDS, Malaria, and Tuberculosis	The Global Fund is a partnership organization designed to accelerate the end of AIDS, tuberculosis, and malaria as epidemics. Founded in 2002, the Global Fund is a partnership between governments, civil society, the private sector, and people affected by the diseases. The Global Fund raises and invests nearly US $4 billion a year to support programs run by local experts in countries and communities most in need
The Food and Agriculture Organization of the United Nations	Pesticide Management is an activity carried out within the overall framework of the Plant Protection Service of UNFAO. It is designed to work together with member countries as a partner to introduce sustainable and environmentally sound agricultural practices that reduce health and environmental risks associated with the use of pesticides. The environmental and health impact of pesticides is being reduced through the implementation of several concrete programs on pesticide management, including residue analysis, product standards setting and methods to analyze them, prevention of accumulation of obsolete stocks of pesticides and means to dispose them, and exchange of information on national actions taken to control pesticides.
Insecticide Resistance Action Committee	The Insecticide Resistance Action Committee is an inter-company organization that operates as a Specialist Technical Group under the umbrella of CropLife International. It was formed in 1984 to provide a coordinated crop protection industry response to prevent or delay the development of resistance in insect and mite pests. The main aims of the Insecticide Resistance Action Committee are firstly to facilitate communication and education on insecticide resistance and secondly to promote the development of resistance management strategies in crop protection and vector control so as to maintain efficacy and support sustainable agriculture and improved public health.
CropLife International	"CropLife is the global federation representing the plant science industry. It supports a network of regional and national associations in 91 countries and its membership includes the major R&D companies as well as a large part of the post-patent and generic pesticide industry. The membership's interests cover crop protection, public health, plant biotechnology and seed production. CropLife International promotes the benefit of crop protection, public health and biotechnology products, their importance to sustainable agriculture, food production and public health, and their responsible use through stewardship activities." (Bernhard Johnen)

7.0 PUBLIC CONSULTATION

Prior to developing this PEA update, USAID prepared an annotated outline describing the organization and content changes to the document and disseminated, for feedback, to key stakeholders (e.g., key USAID users of the PEA, manufacturers, USEPA, etc.). The scoping process, in compliance with USAID Regulation 216, was carried out to facilitate a more efficient PEA preparation process and to define the issues and alternatives that would be examined in detail in the environmental assessment. Annex A contains the compiled feedback from the scoping exercise, as well as USAID's response to each comment.

In addition, USAID posted a draft of the PEA for public comment over a two week period on www.pmi.gov. Key stakeholders were notified in advance of the posting. Annex O contains all comments received during this period, as well as USAID's response to the questions/issues raised. If there were any areas of disagreement, they were noted.

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ANNEXES

Annex A –Compiled Feedback from the Scoping Exercise

Annex B – Environmental Compliance Processes for IRS

Annex C – Detailed Risk Assessment Results

Annex D – Physical-Chemical Properties

Annex E – Pesticide Use and Toxicological Profiles

Annex F – Equations Used to Calculate Exposure and Human Health Risk

Annex G – Worked Examples of the Human Health Risk Assessment Process

Annex H – Worked Examples of the Ecological Risk Assessment Process

Annex I – USAID Environmental Procedures (22 CFR 216)

Annex J – Guidance for Developing SEAs for Malaria Vector Control Programs

Annex K – Recommended IRS Mitigation Measures

Annex L – Recommended LLIN Mitigation Measures

Annex M – Recommended Larvicidal Agent Mitigation Measures

Annex N – Organophosphate Biomonitoring Results

Annex O – Compiled Feedback from the Public Review

Annex P – Climate Change

ANNEX A: COMPILED FEEDBACK FROM THE SCOPING EXERCISE

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
1. Should there be a brief overview of relevant international conventions? (*USAID Regional Environmental Officer*)	Yes; this information is included in Section 6.
2. Will the revised PEA delineate commodities such as LLINs, treated curtains, etc., that USAID will support compared to those that are recommended by the UN/WHOPES? For instance, some LLIN brands that have received interim or full recommendation by WHOPES based on its equivalency policy are not supported by USAID/PMI. (*USAID Regional Environmental Officer*)	Yes; this information is included in Sections 2 and 4. In summary, the PEA reviews insecticides, their concentrations, and their formulations (and netting material, for LLINs). Therefore, although certain tables contain product names and manufacturers' names, the PEA does not endorse products, but rather reviews the safety of product types (e.g., a net with made of x material with x dosage of x AI). Environmental safety is one component of the decision making process for procurements, but not the only consideration.
3. Should the draft outline be circulated to MEOs and REOs as they are key folks who will have to ensure revised PEA is implemented. (*USAID Regional Environmental Officer*)	Yes; MEOs and REOs were included in the solicitation of feedback for the annotated outline.
4. Pleased to see IVM focus/language (*Implementing Partner*)	**n/a**
5. Pleased to see modularization (*Implementing Partner*)	**n/a**
6. Pleased to see inclusion of all larvicides: This also makes good sense given the emerging interest in *Aedes* control, and the likelihood at some point that there will be a demand from missions for more integrated, cross-disease "mosquito control" activities. (*Implementing Partner)*	**n/a**
7. There are older products within the existing WHOPES recommended list for which no up-to-date Human Risk Assessment has been carried out according to the WHO Generic Risk Assessment Model (GRAM, rev Feb 2011). We, as the WHO specification holding company, took the decision to carry out such HRA according to the GRAM two products.. Our conclusions, validated by WHO, supported the continuous use of one product, but not for another.. We therefore applaud harmonization on the methodology but also use this example to encourage dialogue between PMI and WHOPES on the future MVC-PEA risk assessment outcomes and potential relevance to the actual list of WHOPES	USAID agrees that continued dialogues with WHOPES (or a WHOPES-equivalent) will remain critical. The modularization of this PEA and harmonization between the WHO GRAM and the HHRA employed in the PEA's analysis will help facilitate that dialogue.

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
recommended formulations (*Manufacturer*)	
8. Somewhere, include USAID's body of experience with disposal or disposition of obsolete or no longer effective pesticide stocks (esp. DDT), including strategies for re-location of stocks to places where resistance has not yet arisen. (*USAID Environmental Policy Advisor*)	Section 5 contains an IRS mitigation measure for how to handle expired/soon-to-expire insecticide stocks. The PEA will not include a section on experience with disposition of obsolete pesticide stocks. USAID, through PMI, has supported the disposal of DDT in Ethiopia for stocks accumulated prior to PMI. There are lengthy documents describing the process, including a formal work plan, but these materials are not included given it was a one-time activity and PMI has not used DDT since 2012.
9. Will the revised PEA be good through the date proscribed for its predecessor from 2012 (which is March 2018) or it will come with its own shelf-life? (*USAID Technical Officer*)	The PEA will be good for five years from the signed date (i.e., 2016 – 2021).
10. Should USG applicable legislation, other than 22 CFR 216 (NEPA), be discussed in a little bit detail? (USAID Regional Environmental Officer)	Section 7 will address 216 as well as international treaties (e.g., Stockholm, Basel), similar to previous PEA versions.
11. Will the PEA address climate change and ecosystem services, as Executive Order 13677 and the White House Memo should be covered by the revision? (*USAID Regional Environmental Officer*)	Climate change, with revised language to include EO 13677, is included in Annex M.
12. I would also like to see PEA robustly address the issue of safer collection and disposal of the hundred of millions of LLINs that are have already been provided through PMI, other USAID entities and USG as a whole. I would like to see the revised PEA discuss in greater detail the methodologies it will propose to bolster collaborations and coordination among international partners that are heavily involved in LLIN distributions to also join forces to address the safe, effective and economical means of disposal (WB did fund a study on means and ways to address LLIN collection and disposal issues) (*USAID Technical Officer*)	Section 5, "Environmental Management Response", was significantly revised to include language on LLIN misuse, repurposing, and disposal. Results from the World Bank study are included, and they helped the WHO form the basis of their guidelines for sound management of ITNs/LLINs.
13. Will the revised PEA discuss sufficiently the approaches in LLIN, LLIT materials, IRS operations under disaster/emergency vs more of preventive intervention in a development context? (*USAID Technical Officer*)	No; this is outside the scope of the PEA.
14. Under *Intro/PMI section*, what about lessons learned, as well as successes? Please also include progress under RBM (*EPA Officer and USAID Environmental Policy Advisor*)	Malaria control progress under RBM is included in Section 1, and lessons learned from implementation of vector control activities are included under Section 5.

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
15. Suggest including practical resistance management experience and illustrative options, consequences, and decision-support to vector management tools and choices; include maps of progression of resistance to DDT, pyrethroids, Ops, and carbamates. (*USAID Environmental Policy Advisor*)	Section 1, "Resistance Management", was significantly revised to include more practical examples for insecticide resistance, and links were provided to resources such as the Global Plan for Insecticide Resistance Management, resistance data for all PMI focus countries, etc.
16. The **"***Intro/Safety of Interventions"* section is probably the most critical part of the PEA to protect human health and the environment in that it *should* reduce unnecessary exposures to people and their environs. Much attention should be paid to this. (*EPA Officer*)	USAID agrees
17. Will spatial spray be included in new interventions? (*Manufacturer*)	No; IRS, LLINs, larviciding, long lasting insecticidal hammocks, and insecticide-treated clothing will be included in this revised PEA. USAID will add interventions and product types for interventions as they are proven to effective tools for saving lives and cost effective to implement.
18. There is reference to inclusion of insecticides which are still under WHOPES evaluation (but not yet finalized). If the PEA process is completed prior to WHOPES, do you perceive any potential risk of inconsistency in conclusions (even if Risk Assessment methodology is harmonised with WHO)? Also, would a positive PEA for a product which is still under WHOPES evaluation only be intended to support Operational Research within USAID-PMI supported programs? (*Manufacturer*)	These determinations and policies are included in Annex B.
19. Removal of DDT from the PMI toolbox. Based on the agreement reached over 10 years ago in Stockholm Convention on POPs as an international environ treaty, signed in 2001 and effective from May 2004, that aims to eliminate or restrict the production and use of POPs, to phase out the use of DDT in malaria control, after a transition period of five years. (*USAID Environmental Policy Advisor*)	PMI's position on continuing to include DDT as an option, when appropriate, is in alignment with the USG position on use of DDT; this is thoroughly addressed in Section 5. That said, because of insecticide resistance to DDT and the unavailability of quality-assured DDT, USAID, under the PMI, has not supported IRS with DDT since 2012.
20. **Under Alternatives:** Would recommend re-wording to make it clear what are considered alternatives that are versus are not recommended. I would be curious to know when "no action" is an appropriate recommendation, and if there are criteria for selecting the "no action" alternative (for instance, whether there are certain governmental support, logistical, vector susceptibility or other thresholds that have to be in place; otherwise no action would be taken). (*EPA Officer*)	The "no action" option was expanded per suggestion in Section 2.
21. What has been coming out of the IVCC	Alternatives are addressed in Section 2.

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
research pipeline after 10 years? Will the Global IVM PEA capture this, and experiences gained in past 10 years in general? Any disruptive technologies emerging? What about habitat management (e.g., push-pull systems that operate by the simultaneous use of repellent and attractive volatile odorants)? What about baiting and trapping of any value in homes? What about larvivorous fish? (*USAID Environmental Policy Advisor*)	
22. To what extent will the revised PEA discuss goods such as insecticide treated curtains, treated plastic sheeting, personal effects such as blankets and clothing as these have more frequent contacts with subjects than mosquito nets or IRS chemicals? (*USAID Technical Officer*)	Treated clothing and hammocks are addressed in this revised PEA.
23. My assumption is that the WHO paradigm was designed with input from EPA (it looks like it, based on what is outlined here); otherwise, it may be advisable to make sure there aren't inconsistencies between the WHO paradigm and EPA's. (*EPA Officer*)	There are some language differences (mostly semantics), but there is no material difference between the WHO risk assessment paradigm and the EPA risk assessment paradigm.
24. Would it make sense to include "…and other housing improvements"? Eave tubes may be coming into play in the near future, and there is considerable interest in trying to harness the ongoing process of households improving their housing conditions to mosquito control measures. That way this topic is not tied to one specific variety of housing improvement tools, which may or may not fit specific niches. (*Implementing Partn*er)	Eave tubs/housing improvements are not assessed in this PEA (see response to #17).
25. **Under 3.1/Risk Primer:** It is not mentioned what happens after this intentionally conservative approach; usually a tiered approach follows. Please comment. (*Manufacturer*)	This was intentionally not included in previous versions of the PEA, and will not be included in this revision. Rather, if a point estimate indicates a risk (e.g., HQ greater than 1, etc.), then the PEA will use additional information on which to base a conclusion or recommended mitigation measure.
26. Will the hazard assessment endpoints be selected based on EPA/OPP data, when available? (*EPA Officer*)	The PEA includes the hierarchy of endpoints, which indeed often promotes EPA/OPP as the preferred source.
27. For OPs, the biomonitoring work should be discussed under the human health risk characterization and compared to the modeling results. The monitoring data should be used as a validation tool for the modeling. *(EPA Officer*)	The OP biomonitoring study assessed concentrations of pesticide products of metabolism in blood. The risk assessment is based on administered dose, not the comparison with concentrations in blood or urine. Therefore, comparisons cannot be made on this front.
28. Please do clarify the distinction between	This is clarified in Section 3.

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
noncancer hazard and cancer risk. (*Manufacturer*)	
29. Interested to know how/when suppression of nitrogen-fixing bacteria is problematic. We typically don't assess this in pesticide risk assessments at EPA. (*EPA Officer*)	This was just an example of an important function of the soil ecosystem. OPs have been shown to suppress nitrogen-fixing bacteria.
30. The impact on nitrogen-fixing bacteria, and inputs for calculation, may vary for space spray, IRS, LLIN and of course larviciding). (*Manufacturer*)	The exposure concentrations and route of exposure will vary, but not the toxicological data.
31. Will the environmental endpoints be selected based on EPA/OPP data, when available? (*EPA Officer*)	The original PEA, and all subsequent revisions, drew heavily on EPA methodology. This was reiterated in Section 3.
32. Assuming the biomonitoring includes non-target species besides humans, it should be discussed here and compared to the model results. (*EPA Officer)*	The OP biomonitoring study did not include impact on non-target species.
33. When taking into account the two elements of hazard and exposure which contribute to risk; it is common practice within pesticide product registrations to reflect differences in hazard profile between different insecticides (assuming common workplace exposure pathways) through different mitigation measures (ie. variations to PPE recommendations - controlling exposure – with potentially reduced PPE for compounds with lower hazard where it is supported by the Risk Assessment). Currently, as we understand it, the USAID-PMI PPE recommendations for IRS products are the same across all insecticide classes (reflecting general practice recommended by WHO?). As newer compounds, with less hazardous profiles vs older insecticide classes, become recommended for IRS use, does PMI consider the opportunity to potentially save costs in IRS programs through adopting PPE which reflects the specific risk assessment outcomes for those compounds? That could then provide a meaningful context for comparison for IRS programs. (*Manufacturer*)	The BMPs for IRS currently have uniform requirements for PPE, regardless of insecticide type or formulation. This PEA revision did not account different combinations of PPE (coveralls + masks versus coveralls + mask + gloves, etc.). That said, USAID is receptive to adjusting BMPs when it would reduce costs without compromising worker safety. From a programmatic standpoint, it would be important to consider impact on training and compliance, though – if insecticides are rotated annually, for example, and one requires a mask and one doesn't, will compliance with a mask be impacted for the years when needed?
34. Add status of women as applicators (child-bearing age, work-rights issues and dilemmas) (*USAID Environ Policy Advisor*)	Because pregnant women/nursing mothers are particularly susceptible to the toxic effects of pesticide exposure, PMI continues to prohibit these groups from handling pesticides in the course of an IRS campaign. Mitigation measures to this effect are included in Section 5.1. Work-rights issues are beyond the scope of this PEA, but are touched on in PMI's IRS BMP Manual.
35. **Under mitigation measures, ensure sufficient attention to** waste management of spent bed nets and disposal of containers); importance of	As previously noted, Section 5 was significantly revamped and includes detailed information on bed net waste. Section 5 also includes a list of

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
independent field inspections; mention of EMMPs (including measures and frequency). (*USAID Bureau Environmental Officers and Environmental Policy Advisor*)	mitigation measure by intervention.
36. Include status of USEPA registration of vector control products and relationship to WHOPES, PQP, etc. (*USAID Environmental Policy Advisor)*	This information is included in Sections 1 and 2.

ANNEX B. ENVIRONMENTAL COMPLIANCE PROCESSES FOR INDOOR RESIDUAL SPRAYING

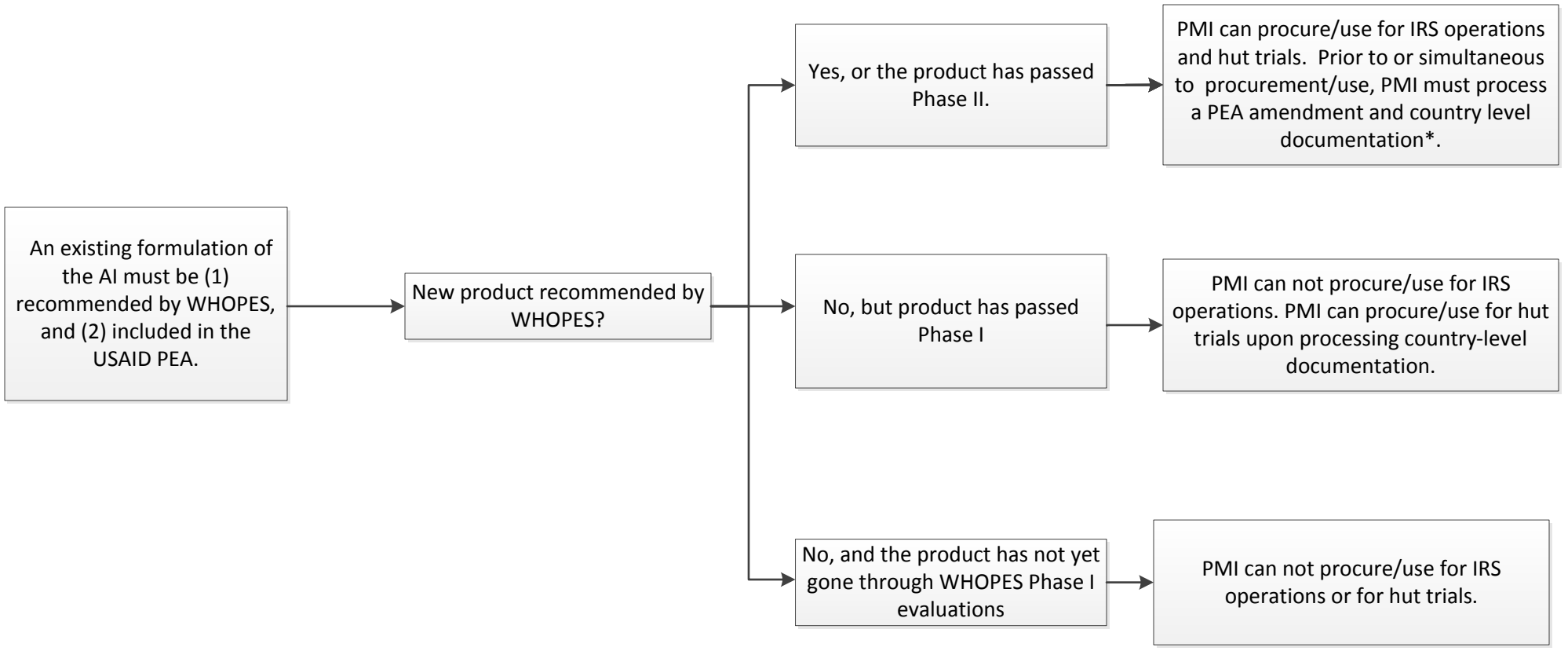
GENERAL NOTES:

(1) Methods for using huts to determine insecticide efficacy are articulated by WHOPES (see http://apps.who.int/iris/bitstream/10665/80270/1/9789241505277_eng.pdf). For the purpose of this annex, a hut trial is the application of insecticide to twelve or less huts (twelve was derived at by assuming that four types of surfaces would be used – mud/cement untreated, mud/cement painted, wood, and straw – by insecticides) to compare residual efficacy and entomologic indicators such as biting rate, density, etc.
(2) "Procure" and "use" are both listed in case PMI ever decided to use a host country government- or other donor-procured insecticide.

ACRONYMS

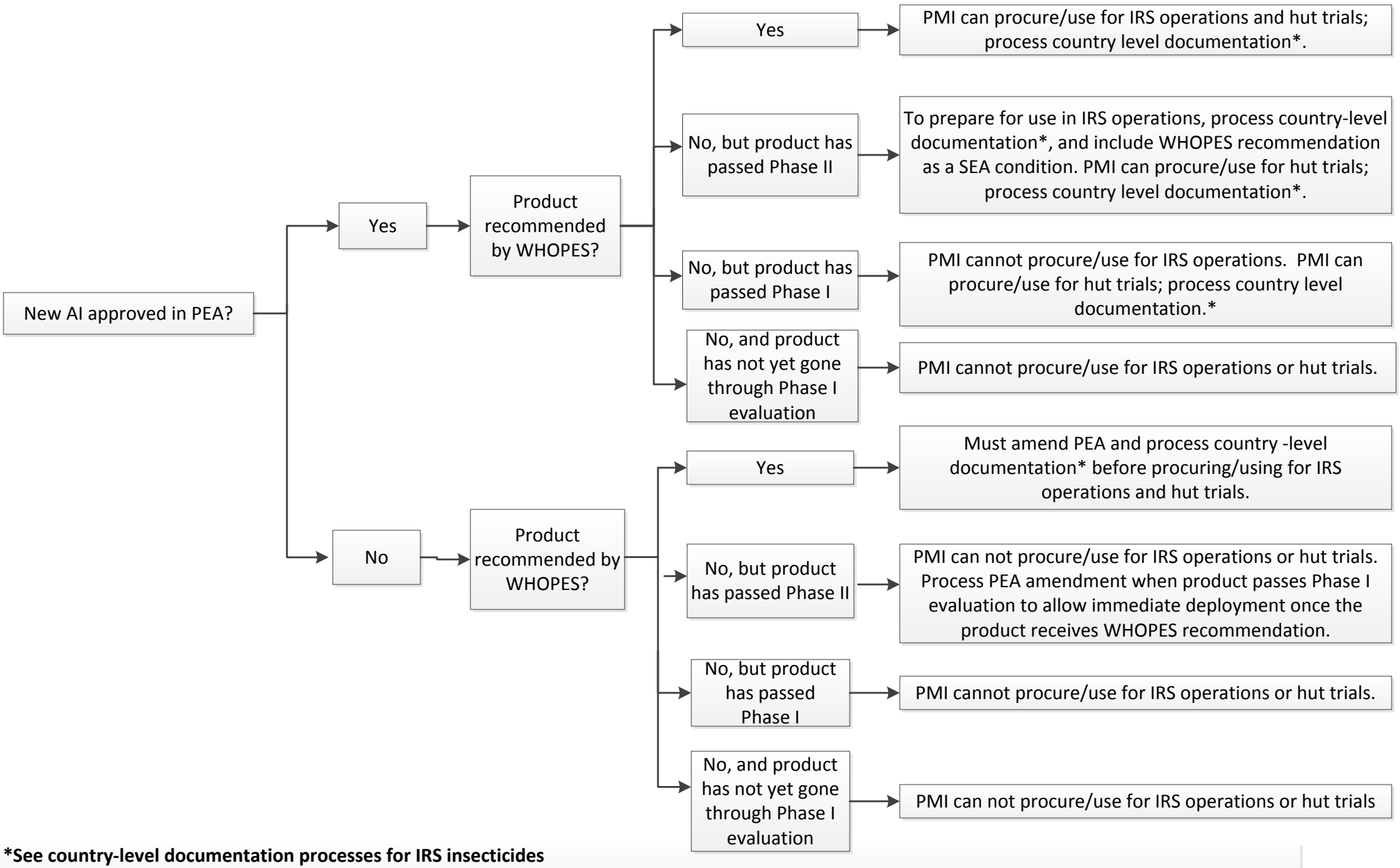
AI: Active ingredient
BCC: Behavior change and communication
BMP: Best management practice
ESAC: External Scientific Advisory Committee
G2G: Government to government
IP: Implementing partner
IRS: Indoor residual spraying
IVCC: Innovative Vector Control Consortium
NMCP: National Malaria Control Program
PMI: President's Malaria Initiative
PEA: Programmatic environmental assessment
SEA: Supplementary environmental assessment
TA: Technical assistance
TOT: Training of trainers
WHOPES: World Health Organization Pesticide Evaluation Scheme

Scenario 1: Use of New Formulations of Existing Active Ingredients for IRS



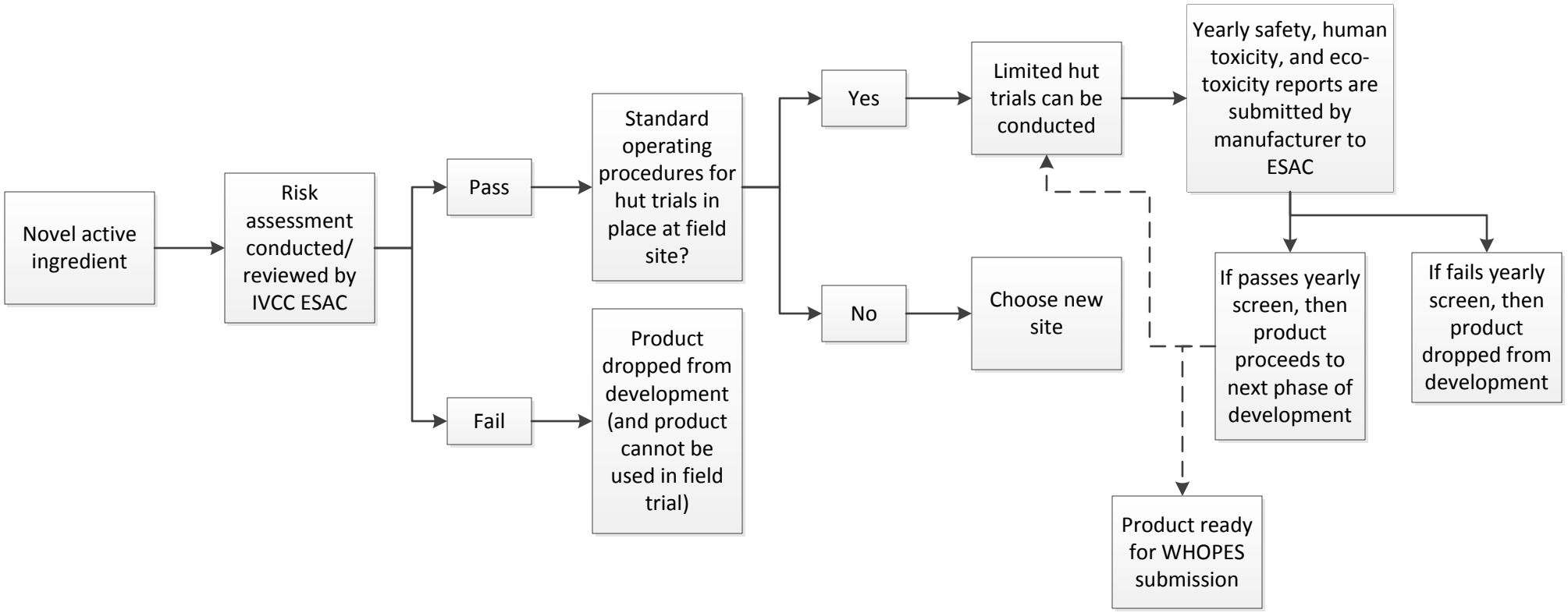
***See country-level documentation processes for IRS insecticides**

Scenario 2: Use of Products with New AIs for IRS



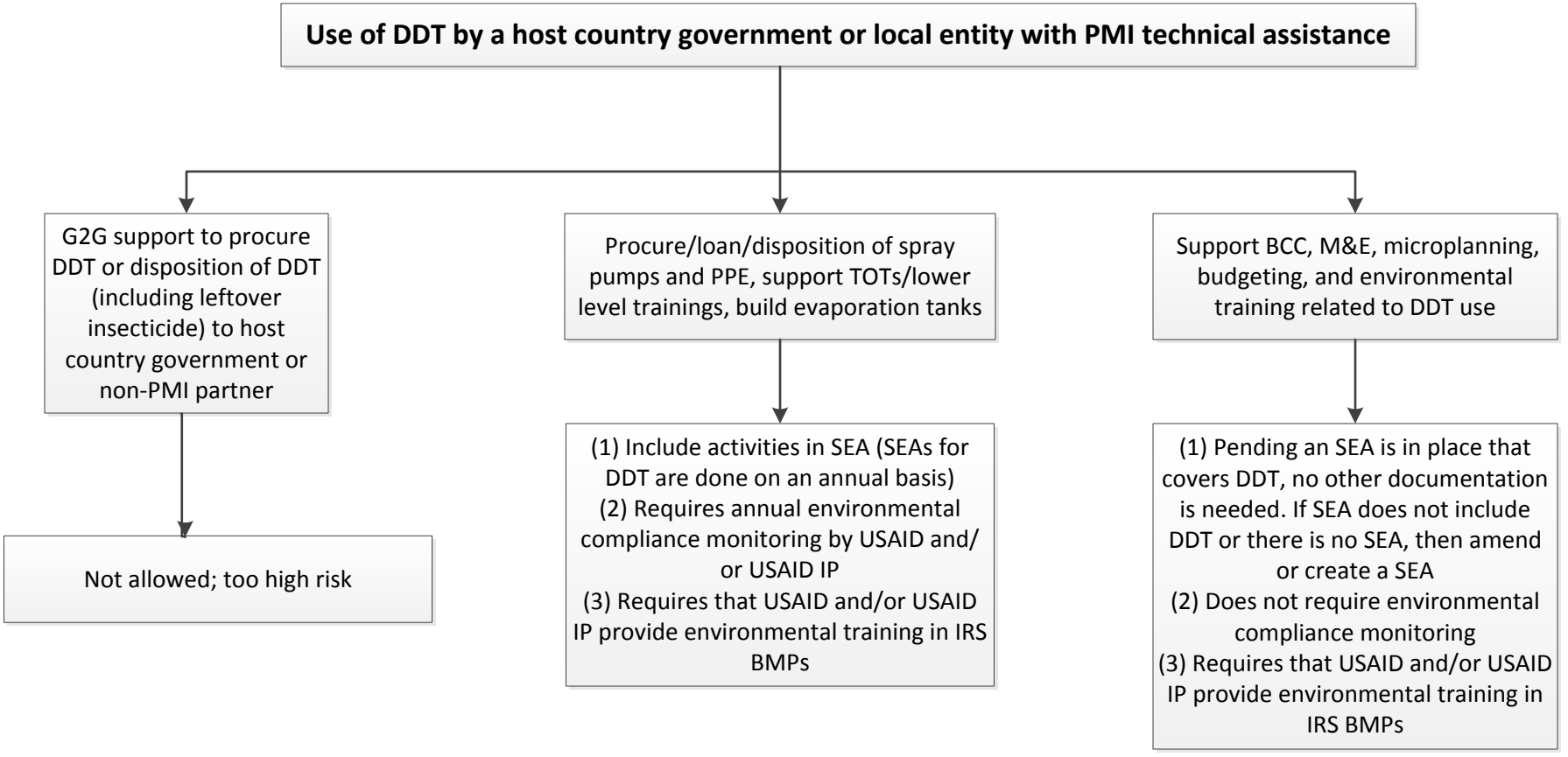
***See country-level documentation processes for IRS insecticides**

Scenario 3: Use of Novel Insecticides (for IRS, LLINs, or vector control technologies) under development by Innovative Vector Control Consortium (IVCC) Partnership

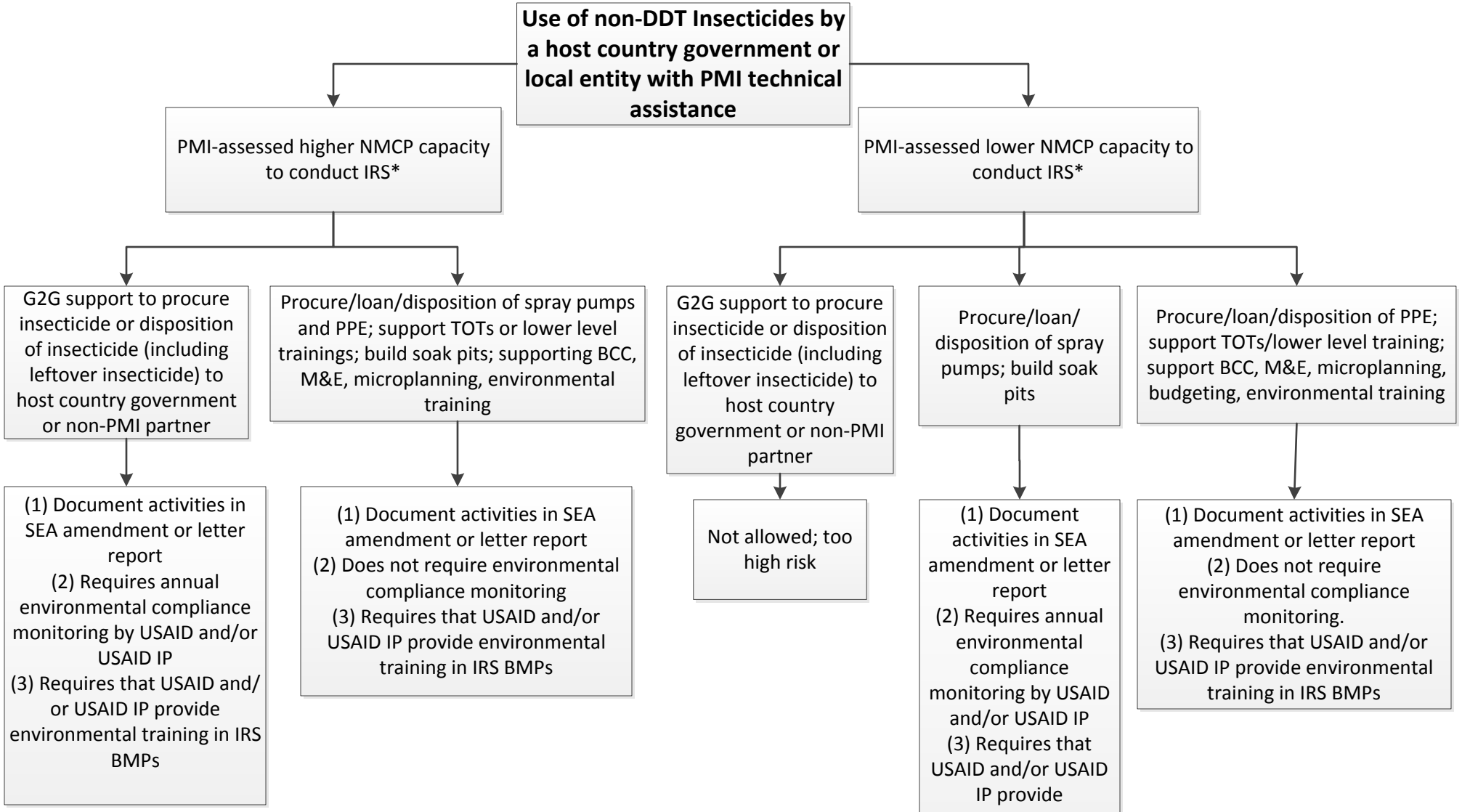


USAID supports insecticide product development through the Innovative Vector Control Consortium (IVCC). The IVCC project proposal process for new vector control products includes a requirement to declare toxicology, eco-toxicology, risk assessment and regulatory information at all stages in the process. All manufacturer-generated safety and toxicity data are submitted to the IVCC External Scientific Advisory Committee (ESAC), who independently review The data and data from other sources and judge whether they have confidence that the final product produced by the project will pass a WHOPES risk assessment for that product category. The ESAC reviews data submitted by the proposer and data from other sources to provide advice on whether the final product is likely to meet the necessary regulatory requirements at the end of the project. In this manner, the IVCC ESAC plays the role that WHOPES plays during a Phase I assessment. The *Safety, Risk Assessment, Toxicology and Eco-Toxicology Procedures Implementation Report* describes the measures that IVCC utilizes to ensure that the insecticide active ingredients and products In development are safe to people and the environment.

Scenario 4: PMI Technical Assistance and Support for an IRS Program Using DDT

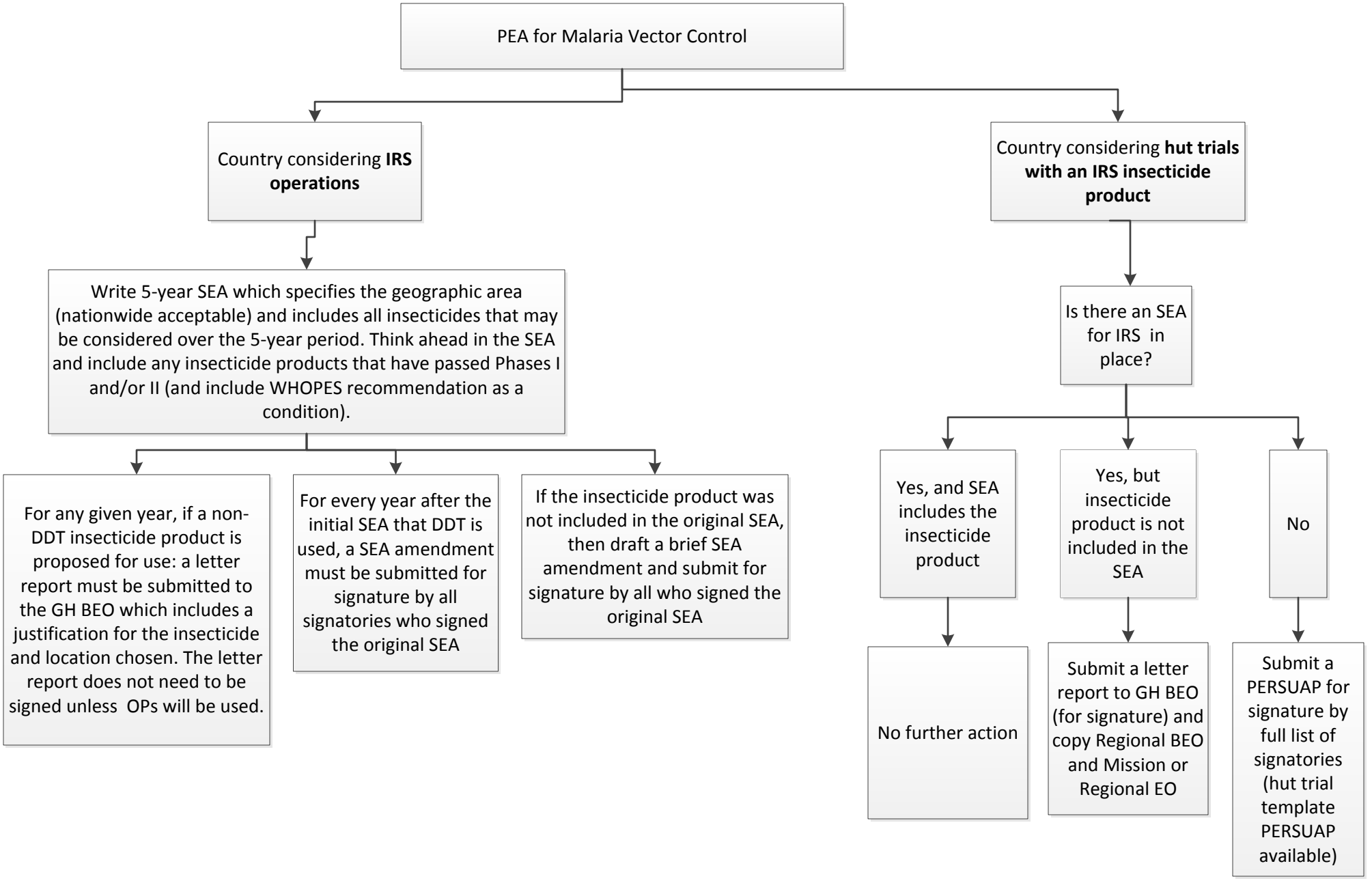


Scenario 5: PMI Technical Assistance and Support for an IRS Program



*NMCP capacity is defined as either higher or lower based on relative experience with IRS programs, implementing partner's capacity assessments, and USAID experience (e.g., historical willingness to comply with environmental regulations, engagement by host-country environmental agency, history of incidents of theft/leakage, and engagement/ leadership by the NMCP in IRS operations and decision-making). As countries gain more experience, more countries are likely going to become higher capacity countries in the context of IRS. Prior to development of IRS country work plans, the USAID IRS Management Team will assess capacity using the criteria just listed.

Country Level Documentation Processes for IRS Insecticide Products



ANNEX C1: DETAILED RISK RESULTS, CURRENT ASSESSMENT

Table C1-1a. Chronic Hazard Quotients:
Indoor Residual Spraying, Mixing/Loading and Spraying, Worker (Scenarios W-IRS-1–6)

Product / Active Ingredient	Worker Mixing/Loading Dermal *With PPE*	Worker Spraying Dermal *With PPE*	Worker Spraying Inhalation *With PPE*	**Worker Total *With PPE***	Worker Mixing/Loading Dermal *No PPE*	Worker Spraying Dermal *No PPE*	Worker Spraying Inhalation *No PPE*	**Worker Total *No PPE***
Chlorfenapyr 240 SC (Phantom)	8.8E-06	7.7E-05	4.0E-05	**0.00013**	0.00029	0.0033	8.0E-04	**0.0044**
Chlothianidin (Sumishield)	1.40E-06	0.00049	0.00013	**0.00062**	7.10E-05	0.021	0.0025	**0.024**
Chlothianidin (Fludora Fusion)	0	0.00033	8.5E-05	**0.00041**	0	0.014	0.0017	**0.016**
Deltamethrin (Fludora Fusion)	0	4.0E-08	2.1E-05	**2.1E-05**	0	1.7E-06	0.00041	**0.00042**
Fludora Fusion (Total)	**0**	**0.00033**	**0.00011**	**0.00043**	**0**	**0.014**	**0.0021**	**0.016**
Pirimiphos-methyl (Actellic 300CS)	0	0.023	0.0059	**0.029**	0	0.99	0.12	**1.1**

Table C1-1b. Chronic Hazard Quotients:
Indoor Residual Spraying, Post-application, Residents (Scenarios R-IRS-1–9)

Product / Active Ingredient	Adult Dermal	Adult Inhalation	**Adult Total**	Child Dermal	Child Inhalation	**Child Total**
Chlorfenapyr 240 SC (Phantom)	0.014	0.00025	**0.014**	0.025	0.00048	**0.026**
Chlothianidin (Sumishield)	0.089	9.7E-06	**0.089**	0.16	1.9E-05	**0.16**
Chlothianidin (Fludora Fusion)	0.059	9.7E-06	**0.059**	0.11	1.9E-05	**0.11**
Deltamethrin (Fludora Fusion)	7.3E-06	3.5E-05	**4.2E-05**	1.3E-05	6.9E-05	**8.2E-05**
Fludora Fusion (Total)	**0.059**	**4.5E-05**	**0.059**	**0.11**	**8.8E-05**	**0.11**
Pirimiphos-methyl (Actellic 300CS)	4.1	2.5	**6.7**	7.5	5.0	**12**

Product / Active Ingredient	**Toddler Dermal**	**Toddler Inhalation**	**Toddler Hand-mouth**	**Toddler Total**	**Infant Inhalation**	**Infant Breast Milk**	**Infant Total**
Chlorfenapyr 240 SC (Phantom)	0.11	0.0012	0.019	**0.13**	0.0023	0.0024	**0.0047**

Product / Active Ingredient	Toddler Dermal	Toddler Inhalation	Toddler Hand-mouth	Toddler Total	Infant Inhalation	Infant Breast Milk	Infant Total
Chlothianidin (Sumishield)	0.73	4.8E-05	0.062	**0.79**	9.3E-05	0.90	**0.90**
Chlothianidin (Fludora Fusion)	0.48	4.8E-05	0.041	**0.52**	9.3E-05	0.60	**0.60**
Deltamethrin (Fludora Fusion)	5.9E-05	0.00017	0.010	**0.010**	0.00034	0.031	**0.031**
Fludora Fusion (Total)	**0.48**	**0.00022**	**0.051**	**0.53**	**0.00043**	**0.63**	**0.63**
Pirimiphos-methyl (Actellic 300CS)	34	13	2.9	**49**	24	0.48	**25**

Table C1-2a. Chronic Hazard Quotients: Long-lasting Insecticidal Nets, Sleeping, Residents (Scenarios R-LLIN-1–13)

Product / Active Ingredient	Adult Dermal	Adult Inhalation	Adult Total	Child Dermal	Child Inhalation	Child Total
Alpha-cypermethrin (Interceptor G2)	0.16	0.0035	**0.17**	0.19	0.0072	**0.20**
Chlorfenapyr (Interceptor G2)	0.15	8.3E-05	**0.15**	0.18	0.00017	**0.18**
Interceptor G2 (Total)	**0.32**	**0.0036**	**0.32**	**0.37**	**0.0074**	**0.38**
Alpha-cypermethrin (Royal Guard)	0.37	0.0035	**0.37**	0.44	0.0072	**0.44**
Pyriproxyfen (Royal Guard)	0.025	1.2E-05	**0.025**	0.030	2.4E-05	**0.030**
Royal Guard (Total)	**0.40**	**0.0035**	**0.40**	**0.47**	**0.0073**	**0.47**
Alpha-cypermethrin (Royal Sentry)	0.43	0.0035	**0.43**	0.51	0.0072	**0.51**
Permethrin (Olyset Duo)	0.0063	2.4E-05	**0.0063**	0.0075	4.9E-05	**0.0075**
Pyriproxyfen (Olyset Duo)	0.045	1.2E-05	**0.045**	0.053	2.4E-05	**0.053**
Olyset Duo (Total)	**0.051**	**3.6E-05**	**0.051**	**0.061**	**7.3E-05**	**0.061**
Permethrin (Olyset Plus)	0.0063	2.4E-05	**0.0063**	0.0075	4.9E-05	**0.0075**
Piperonyl Butoxide (Olyset Plus)	NA	0.0018	**0.0018**	NA	0.0037	**0.0037**
Olyset Plus (Total)	**0.0063**	**0.0018**	**0.0081**	**0.0075**	**0.0037**	**0.011**
Deltamethrin (Panda Net 2.0)	3.0E-04	1.2E-05	**0.00031**	0.00035	2.4E-05	**0.00038**

Product / Active Ingredient	Toddler Dermal	Toddler Inhalation	Toddler Hand-mouth	Toddler Direct Oral	Toddler Total
Alpha-cypermethrin (Interceptor G2)	0.27	0.020	0.23	2.0	**2.5**
Chlorfenapyr (Interceptor G2)	0.25	0.00046	0.11	0.91	**1.3**
Interceptor G2 (Total)	**0.51**	**0.020**	**0.33**	**2.9**	**3.7**
Alpha-cypermethrin (Royal Guard)	0.60	0.020	0.51	4.4	**5.6**
Pyriproxyfen (Royal Guard)	0.041	6.7E-05	0.0088	0.076	**0.13**
Royal Guard (Total)	**0.64**	**0.020**	**0.52**	**4.5**	**5.7**
Alpha-cypermethrin (Royal Sentry)	0.69	0.020	0.60	5.1	**6.4**
Permethrin (Olyset Duo)	0.010	0.00013	0.044	0.38	**0.43**
Pyriproxyfen (Olyset Duo)	0.073	6.7E-05	0.016	0.13	**0.22**
Olyset Duo (Total)	**0.083**	**2.0E-04**	**0.060**	**0.51**	**0.65**
Permethrin (Olyset Plus)	0.010	0.00013	0.044	0.38	**0.43**
Piperonyl Butoxide (Olyset Plus)	NA	0.010	0.034	0.29	**0.34**
Olyset Plus (Total)	**0.010**	**0.010**	**0.078**	**0.67**	**0.77**
Deltamethrin (Panda Net 2.0)	0.00049	6.6E-05	0.21	1.8	**2.0**

Product / Active Ingredient	Infant Dermal	Infant Inhalation	Infant Hand-mouth	Infant Direct Oral	Infant Breast Milk	Infant Total
Alpha-cypermethrin (Interceptor G2)	0.36	0.050	0.31	5.7	0.22	**6.7**
Chlorfenapyr (Interceptor G2)	0.33	0.0012	0.14	2.6	0.025	**3.1**
Interceptor G2 (Total)	**0.70**	**0.051**	**0.46**	**8.4**	**0.25**	**9.8**
Alpha-cypermethrin (Royal Guard)	0.82	0.050	0.70	13	0.49	**15**
Pyriproxyfen (Royal Guard)	0.056	0.00017	0.012	0.22	0.054	**0.34**
Royal Guard (Total)	**0.87**	**0.050**	**0.72**	**13**	**0.54**	**15**
Alpha-cypermethrin (Royal Sentry)	0.95	0.050	0.82	15	0.57	**17**
Permethrin (Olyset Duo)	0.014	0.00034	0.060	1.1	0.009	**1.2**

Product / Active Ingredient	Infant Dermal	Infant Inhalation	Infant Hand-mouth	Infant Direct Oral	Infant Breast Milk	Infant Total
Pyriproxyfen (Olyset Duo)	0.10	0.00017	0.021	0.39	0.097	**0.61**
Olyset Duo (Total)	**0.11**	**5.0E-04**	**0.081**	**1.5**	**0.11**	**1.8**
Permethrin (Olyset Plus)	0.014	0.00034	0.060	1.1	0.009	**1.2**
Piperonyl Butoxide (Olyset Plus)	NA	0.025	0.047	0.86	0.21	**1.1**
Olyset Plus (Total)	**0.014**	**0.025**	**0.11**	**2.0**	**0.22**	**2.3**
Deltamethrin (Panda Net 2.0)	0.00066	0.00017	0.29	5.2	1.3	**6.8**

Table C1-2b. Incremental Cancer Risk: Long-lasting Insecticidal Nets, Sleeping, Residents (Scenarios R-LLIN-1–13)

Product / Active Ingredient	Adult Dermal	Adult Inhalation	Adult Total	Child Dermal	Child Inhalation	Child Total
Permethrin (Olyset Duo)	2.4E-04	2.0E-08	2.4E-04	3.6E-05	5.2E-09	**3.6E-05**

Product / Active Ingredient	Toddler Dermal	Toddler Inhalation	Toddler Hand-mouth	Toddler Direct Oral	Toddler Total
Permethrin (Olyset Duo)	4.9E-05	1.4E-08	1.1E-05	9.1E-05	**1.5E-04**

Product / Active Ingredient	Infant Dermal	Infant Inhalation	Infant Hand-mouth	Infant Direct Oral	Infant Breast Milk	Infant Total
Permethrin (Olyset Duo)	1.3E-05	7.1E-09	2.9E-06	5.3E-05	4.3E-07	**6.9E-05**

Table C1-2c. Chronic Hazard Quotients:
Long-lasting Insecticidal Nets, Net Washing, Residents (Scenarios R-LLIN-14–18)

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	Adult Total	Child Dermal	Child Hand-mouth	Child Total	Infant Breast Milk (only pathway)
Alpha-cypermethrin (Interceptor G2)	0.0055	0.0057	**0.011**	0.0059	0.0064	**0.012**	**0.014**
Chlorfenapyr (Interceptor G2)	0.005	0.0026	**0.0077**	0.0055	0.0029	**0.0084**	**0.0013**
Interceptor G2 (Total)	**0.011**	**0.0083**	**0.019**	**0.011**	**0.0093**	**0.021**	**0.016**
Alpha-cypermethrin (Royal Guard)	0.012	0.013	**0.025**	0.013	0.014	**0.028**	**0.033**

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	**Adult Total**	Child Dermal	Child Hand-mouth	**Child Total**	**Infant Breast Milk (only pathway)**
Pyriproxyfen (Royal Guard)	0.00084	0.00022	**0.0011**	0.00092	0.00025	**0.0012**	**0.0023**
Royal Guard (Total)	**0.013**	**0.013**	**0.026**	**0.014**	**0.015**	**0.029**	**0.035**
Alpha-cypermethrin (Royal Sentry)	0.014	0.015	**0.029**	0.016	0.017	**0.032**	**0.038**
Permethrin (Olyset Duo)	0.00021	0.0011	**0.0013**	0.00023	0.0012	**0.0014**	**0.00038**
Pyriproxyfen (Olyset Duo)	0.0015	0.00039	**0.0019**	0.0016	0.00044	**0.0021**	**0.0040**
Olyset Duo (Total)	**0.0017**	**0.0015**	**0.0032**	**0.0019**	**0.0017**	**0.0035**	**0.0044**
Permethrin (Olyset Plus)	0.00021	0.0011	**0.0013**	0.00023	0.0012	**0.0014**	**0.00038**
Piperonyl Butoxide (Olyset Plus)	NA	0.00085	**0.00085**	NA	0.00095	**0.00095**	**0.0088**
Olyset Plus (Total)	**0.00021**	**0.0019**	**0.0021**	**0.00023**	**0.0022**	**0.0024**	**0.0092**
Deltamethrin (Panda Net 2.0)	1.0E-05	0.0052	**0.0052**	1.1E-05	0.0058	**0.0058**	**0.054**

Table C1-2d. Incremental Cancer Risk: Long-lasting Insecticidal Nets, Net Washing, Residents (Scenarios R-LLIN-14–18)

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	**Adult Total**	Child Dermal	Child Hand-mouth	**Child Total**	**Infant Breast Milk (only pathway)**
Permethrin (Olyset Duo)	2.0E-07	5.2E-08	**2.5E-07**	2.2E-07	5.9E-08	**2.8E-07**	**1.8E-08**

Table C1-2e Acute Hazard Quotients: Long-lasting Insecticidal Nets, Net Washing, Residents (Scenarios R-LLIN-19–22)

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	**Adult Total**	Child Dermal	Child Hand-mouth	**Child Total**
Alpha-cypermethrin (Interceptor G2)	0.0014	0.019	**0.020**	0.0016	0.021	**0.022**
Chlorfenapyr (Interceptor G2)	0.014	0.0082	**0.023**	0.016	0.0093	**0.025**
Interceptor G2 (Total)	**0.016**	**0.027**	**0.043**	**0.017**	**0.030**	**0.047**
Alpha-cypermethrin (Royal Guard)	0.0032	0.042	**0.045**	0.0035	0.047	**0.051**
Pyriproxyfen (Royal Guard)	NA	0.0042	**0.0042**	NA	0.0047	**0.0047**

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	**Adult Total**	Child Dermal	Child Hand-mouth	**Child Total**
Royal Guard (Total)	**0.0032**	**0.046**	**0.049**	**0.0035**	**0.052**	**0.055**
Alpha-cypermethrin (Royal Sentry)	0.0038	0.048	**0.052**	0.0041	0.055	**0.059**
Permethrin (Olyset Duo)	0.011	0.059	**0.071**	0.012	0.067	**0.079**
Pyriproxyfen (Olyset Duo)	NA	0.0074	**0.0074**	NA	0.0084	**0.0084**
Olyset Duo (Total)	**0.011**	**0.067**	**0.078**	**0.012**	**0.075**	**0.088**
Permethrin (Olyset Plus)	0.011	0.059	**0.071**	0.012	0.067	**0.079**
Piperonyl Butoxide (Olyset Plus)	NA	0.0083	**0.0083**	NA	0.0094	**0.0094**
Olyset Plus (Total)	**0.011**	**0.068**	**0.079**	**0.012**	**0.076**	**0.089**
Deltamethrin (Panda Net 2.0)	0.00055	0.28	**0.28**	0.00059	0.32	**0.32**

Table C1-3a. Chronic Hazard Quotients: Larvicides, Mixing/Loading and Spraying, Worker (Scenarios W-Larv-1–4)

Product / Active Ingredient	Worker Mixing/Loading Dermal With PPE	Worker Spraying Dermal With PPE	**Worker Total With PPE**	Worker Mixing/Loading Dermal No PPE	Worker Spraying Dermal No PPE	**Worker Total No PPE**
Chlorpyrifos	2.7E-07	7.9E-06	**8.2E-06**	9.1E-06	0.00034	**0.00035**
Diflubenzuron (DT)	2.5E-09	2.8E-06	**2.8E-06**	1.3E-07	0.00012	**0.00012**
Diflubenzuron (G)	2.5E-09	2.8E-06	**2.8E-06**	1.3E-07	0.00012	**0.00012**
Diflubenzuron (WP)	1.1E-06	2.8E-06	**3.9E-06**	5.5E-05	0.00012	**0.00018**
Fenthion	0.00019	0.0055	**0.0056**	0.0063	0.24	**0.24**
Methoprene	1.2E-08	3.4E-07	**3.5E-07**	3.9E-07	1.5E-05	**1.5E-05**
Novaluron	3.6E-06	1.0E-04	**0.00011**	0.00012	0.0045	**0.0046**
Pirimiphos-methyl	0.00028	0.0081	**0.0084**	0.0094	0.35	**0.36**
Pyriproxyfen	5.6E-08	1.6E-06	**1.7E-06**	1.9E-06	7.1E-05	**7.3E-05**
Spinosad (all formulations)	NA	NA	**NA**	NA	NA	**NA**
Temephos (EC)	5.6E-05	0.0016	**0.0017**	0.0019	0.070	**0.072**
Temephos (G)	1.4E-06	0.0016	**0.0016**	7.1E-05	0.070	**0.070**

Table C1-3b. Chronic Hazard Quotients: Larvicides, Ground Water Exposures, Residents (Scenarios R-Larv-1–8)

Product / Active Ingredient	Adult Ground Water Ingestion	Adult Ground Water Dermal	**Adult Total**	Child Ground Water Ingestion	Child Ground Water Dermal	**Child Total**
Chlorpyrifos	0.00014	2.6E-08	**0.00014**	0.00014	3.3E-08	**0.00014**
Diflubenzuron	2.3E-05	9.8E-09	**2.3E-05**	2.3E-05	1.2E-08	**2.3E-05**
Fenthion	0.022	5.6E-05	**0.022**	0.021	6.9E-05	**0.021**
Methoprene	3.4E-07	1.1E-09	**3.4E-07**	3.3E-07	1.4E-09	**3.3E-07**
Novaluron	4.3E-05	3.6E-07	**4.3E-05**	4.2E-05	4.5E-07	**4.2E-05**
Pirimiphos-methyl	0.0026	2.2E-05	**0.0027**	0.0025	2.8E-05	**0.0026**
Pyriproxyfen	6.4E-07	5.4E-09	**6.5E-07**	6.2E-07	6.7E-09	**6.3E-07**
Spinosad	8.3E-05	NA	**8.3E-05**	8.1E-05	NA	**8.1E-05**
Spinosad 83.3 Monolayer	8.3E-05	NA	**8.3E-05**	8.1E-05	NA	**8.1E-05**
Spinosad 25 Extended Release	6.7E-05	NA	**6.7E-05**	6.4E-05	NA	**6.4E-05**
Temephos	0.00017	5.4E-06	**0.00017**	0.00016	6.7E-06	**0.00017**

Product / Active Ingredient	**Toddler Ground Water Ingestion**	**Toddler Ground Water Dermal**	Toddler Total	**Infant Ground Water Dermal**	**Infant Breast Milk**	Infant Total
Chlorpyrifos	0.00032	4.2E-08	**0.00032**	5.8E-08	0.00031	**0.00031**
Diflubenzuron	5.2E-05	1.6E-08	**5.2E-05**	2.2E-08	5.0E-05	**5.0E-05**
Fenthion	0.049	8.9E-05	**0.049**	0.00012	0.047	**0.047**
Methoprene	7.5E-07	1.8E-09	**7.5E-07**	2.5E-09	7.3E-07	**7.3E-07**
Novaluron	9.5E-05	5.8E-07	**9.6E-05**	8.1E-07	9.3E-05	**9.4E-05**
Pirimiphos-methyl	0.0058	3.6E-05	**0.0059**	4.9E-05	0.00019	**0.00024**
Pyriproxyfen	1.4E-06	8.7E-09	**1.4E-06**	1.2E-08	1.4E-06	**1.4E-06**
Spinosad	0.00018	NA	**0.00018**	NA	1.2E-05	**1.2E-05**
Spinosad 83.3 Monolayer	0.00018	NA	**0.00018**	NA	1.2E-05	**1.2E-05**
Spinosad 25 Extended Release	0.00015	NA	**0.00015**	NA	9.6E-06	**9.6E-06**
Temephos	0.00037	8.6E-06	**0.00038**	1.2E-05	0.00037	**0.00038**

Table C1-3c. Incremental Cancer Risk:
Larvicides, Ground Water Exposures, Residents (Scenarios R-Larv-1–8)

Product / Active Ingredient	Adult Ground Water Ingestion	Adult Ground Water Dermal	**Adult Total**	Child Ground Water Ingestion	Child Ground Water Dermal	**Child Total**
Diflubenzuron; 4-chlorophenylurea metabolite	3.9E-09	3.30E-11	**3.9E-09**	4.80E-10	5.20E-12	**4.80E-10**

Product / Active Ingredient	Toddler Ground Water Ingestion	Toddler Ground Water Dermal	**Toddler Total**	Infant Ground Water Dermal	Infant Breast Milk	**Infant Total**
Diflubenzuron; 4-chlorophenylurea metabolite	1.1E-09	6.70E-12	**1.1E-09**	1.80E-12	2.10E-10	**2.20E-10**

Table C1-4a. Chronic Hazard Quotients:
Treated Hammocks, Sleeping, Residents (Scenarios R-Hamm-1–9)

Product / Active Ingredient	**Adult Dermal (only pathway)**	**Child Dermal (only pathway)**	Toddler Dermal	Toddler Hand-mouth	Toddler Direct Oral	**Toddler Total**
Permethrin	**0.025**	**0.030**	0.039	0.082	0.71	**0.83**
Deltamethrin	**0.00065**	**0.00081**	0.0010	0.22	1.9	**2.1**

Product / Active Ingredient	Infant Dermal	Infant Hand-mouth	Infant Direct Oral	Infant Breast Milk	**Infant Total**
Permethrin	0.054	0.11	2.1	0.035	**2.3**
Deltamethrin	0.0015	0.30	5.5	2.8	**8.6**

Table C1-4b. Incremental Cancer Risk:
Treated Hammocks, Sleeping, Residents (Scenarios R-Hamm-1–9)

Product / Active Ingredient	**Adult Dermal (only pathway)**	**Child Dermal (only pathway)**	Toddler Dermal	Toddler Hand-mouth	Toddler Direct Oral	**Toddler Total**
Permethrin	**9.2E-04**	**1.5E-04**	1.9E-04	2.0E-05	1.7E-04	**3.8E-04**

Product / Active Ingredient	Infant Dermal	Infant Hand-mouth	Infant Direct Oral	Infant Breast Milk	**Infant Total**
Permethrin	5.2E-05	5.4E-06	9.9E-05	1.7E-06	**1.6E-04**

Table C1-4c. Chronic Hazard Quotients:
Treated Hammocks, Washing, Residents (Scenarios R-Hamm-10-14)

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	**Adult Total**	Child Dermal	Child Hand-mouth	**Child Total**	**Infant Breast Milk (only pathway)**
Permethrin	5.6E-05	0.00029	**0.00034**	6.1E-05	0.00032	0.00039	**0.00010**
Deltamethrin	1.5E-06	0.00077	**0.00077**	1.6E-06	0.00087	0.00087	**0.0080**

Table C1-4d. Incremental Cancer Risk:
Treated Hammocks, Washing, Residents (Scenarios R-Hamm-10-14)

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	**Adult Total**	Child Dermal	Child Hand-mouth	**Child Total**	**Infant Breast Milk (only pathway)**
Permethrin	5.4E-08	1.4E-08	**6.8E-08**	5.8E-08	1.6E-08	**7.4E-08**	**4.8E-09**

Table C1-4e. Acute Hazard Quotients:
Treated Hammocks, Washing, Residents (Scenarios R-Hamm-15-18)

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	**Adult Total**	Child Dermal	Child Hand-mouth	**Child Total**
Permethrin	0.0031	0.016	**0.019**	0.0033	0.018	**0.021**
Deltamethrin	8.2E-05	0.042	**0.042**	8.9E-05	0.047	**0.048**

ANNEX C2: DETAILED RISK RESULTS FOR ALL INSECTICIDES

Table C2-1a. Chronic Hazard Quotients:
Indoor Residual Spraying, Mixing/Loading and Spraying, Worker (Scenarios W-IRS-1–6)

Product / Active Ingredient	Worker Mixing/Loading Dermal *With PPE*	Worker Spraying Dermal *With PPE*	Worker Spraying Inhalation *With PPE*	**Worker Total *With PPE***	Worker Mixing/Loading Dermal *No PPE*	Worker Spraying Dermal *No PPE*	Worker Spraying Inhalation *No PPE*	**Worker Total *No PPE***
Chlorfenapyr 240 SC (Phantom)	8.8E-06	7.7E-05	4.0E-05	**0.00013**	0.00029	0.0033	8.0E-04	**0.0044**
Chlothianidin (Sumishield)	1.40E-06	0.00049	0.00013	**0.00062**	7.10E-05	0.021	0.0025	**0.024**
Chlothianidin (Fludora Fusion)	0	0.00033	8.5E-05	**0.00041**	0	0.014	0.0017	**0.016**
Deltamethrin (Fludora Fusion)	0	4.0E-08	2.1E-05	**2.1E-05**	0	1.7E-06	0.00041	**0.00042**
Fludora Fusion (Total)	**0**	**0.00033**	**0.00011**	**0.00043**	**0**	**0.014**	**0.0021**	**0.016**
Pirimiphos-methyl (Actellic 300CS)	0	0.023	0.0059	**0.029**	0	0.99	0.12	**1.1**
Alpha-cypermethrin	2.1E-05	1.7E-05	1.2E-05	**4.9E-05**	0.0011	0.00072	0.00023	**0.002**
Bendiocarb	0.0039	0.0031	0.00052	**0.0075**	0.20	0.13	0.010	**0.34**
Bifenthrin	3.8E-06	3.0E-06	3.9E-05	**4.6E-05**	0.00019	0.00013	0.00078	**0.0011**
Chlorfenapyr	0.00016	0.00012	6.4E-05	**0.00034**	0.0079	0.0053	0.0013	**0.014**
Cyfluthrin	2.4E-07	1.9E-07	0.00073	**0.00073**	1.2E-05	8.1E-06	0.015	**0.015**
DDT	0.018	0.014	0.012	**0.045**	0.92	0.62	0.25	**1.8**
Deltamethrin	4.6E-08	3.6E-08	1.9E-05	**1.9E-05**	2.3E-06	1.6E-06	0.00037	**0.00038**
Etofenprox	0.00011	8.6E-05	8.3E-06	**2.0E-04**	0.0055	0.0037	0.00017	**0.0094**
Fenitrothion	0.0041	0.0032	0.021	**0.028**	0.20	0.14	0.41	**0.76**
Lambda-cyhalothrin	5.1E-06	4.0E-06	0.00013	**0.00014**	0.00026	0.00017	0.0026	**0.0030**
Malathion	8.2E-05	6.4E-05	0.00032	**0.00046**	0.0041	0.0028	0.0064	**0.013**
Pirimiphos-methyl	0.044	0.034	0.0089	**0.087**	2.2	1.5	0.18	**3.9**
Propoxur	3.1E-06	2.4E-06	0.0016	**0.0016**	0.00015	1.0E-04	0.031	**0.031**

Note: For the purpose of this analysis all previously-analyzed products were assumed to be supplied in wettable powder (WP) formulation.

Table C2-1b. Chronic Hazard Quotients:
Indoor Residual Spraying, Post-application, Residents (Scenarios R-IRS-1–9)

Product / Active Ingredient	Adult Dermal	Adult Inhalation	**Adult Total**	Child Dermal	Child Inhalation	**Child Total**
Chlorfenapyr 240 SC (Phantom)	0.014	0.00025	**0.014**	0.025	0.00048	**0.026**
Chlothianidin (Sumishield)	0.089	9.7E-06	**0.089**	0.16	1.9E-05	**0.16**
Chlothianidin (Fludora Fusion)	0.059	9.7E-06	**0.059**	0.11	1.9E-05	**0.11**
Deltamethrin (Fludora Fusion)	7.3E-06	3.5E-05	**4.2E-05**	1.3E-05	6.9E-05	**8.2E-05**
Fludora Fusion (Total)	**0.059**	**4.5E-05**	**0.059**	**0.11**	**8.8E-05**	**0.11**
Pirimiphos-methyl (Actellic 300CS)	4.1	2.5	**6.7**	7.5	5.0	**12**
Alpha-cypermethrin	0.003	0.01	**0.014**	0.0055	0.021	**0.026**
Bendiocarb	0.56	1.5	**2.0**	1.0	2.9	**3.9**
Bifenthrin	0.00054	0.0074	**0.0079**	0.00099	0.014	**0.015**
Chlorfenapyr	0.022	0.00025	**0.023**	0.040	0.00048	**0.041**
Cyfluthrin	3.4E-05	0.00013	**0.00017**	6.1E-05	0.00026	**0.00032**
DDT	2.6	0.044	**2.7**	4.7	0.086	**4.8**
Deltamethrin	6.5E-06	3.5E-05	**4.2E-05**	1.2E-05	6.9E-05	**8.1E-05**
Etofenprox	0.016	8.9E-06	**0.016**	0.028	1.7E-05	**0.028**
Fenitrothion	0.58	3.2	**3.7**	1.1	6.2	**7.2**
Lambda-cyhalothrin	0.00073	0.00033	**0.0011**	0.0013	0.00064	**0.0020**
Malathion	0.012	0.19	**0.21**	0.021	0.38	**0.40**
Pirimiphos-methyl	6.2	2.5	**8.7**	11	5.0	**16**
Propoxur	0.00044	0.20	**0.20**	0.00079	0.38	**0.38**

Product / Active Ingredient	**Toddler Dermal**	**Toddler Inhalation**	**Toddler Hand-mouth**	**Toddler Total**	**Infant Inhalation**	**Infant Breast Milk**	**Infant Total**
Chlorfenapyr 240 SC (Phantom)	0.11	0.0012	0.019	**0.13**	0.0023	0.0024	**0.0047**
Chlothianidin (Sumishield)	0.73	4.8E-05	0.062	**0.79**	9.3E-05	0.90	**0.90**
Chlothianidin (Fludora Fusion)	0.48	4.8E-05	0.041	**0.52**	9.3E-05	0.60	**0.60**

Product / Active Ingredient	Toddler Dermal	Toddler Inhalation	Toddler Hand-mouth	Toddler Total	Infant Inhalation	Infant Breast Milk	Infant Total
Deltamethrin (Fludora Fusion)	5.9E-05	0.00017	0.010	**0.010**	0.00034	0.031	**0.031**
Fludora Fusion (Total)	**0.48**	**0.00022**	**0.051**	**0.53**	**0.00043**	**0.63**	**0.63**
Pirimiphos-methyl (Actellic 300CS)	34	13	2.9	**49**	24	0.48	**25**
Alpha-cypermethrin	0.025	0.052	0.0084	**0.085**	0.10	0.024	**0.12**
Bendiocarb	4.6	7.4	0.39	**12**	14	29	**43**
Bifenthrin	0.0044	0.037	0.0058	**0.047**	0.07	0.023	**0.093**
Chlorfenapyr	0.18	0.0012	0.031	**0.21**	0.0023	0.0038	**0.0061**
Cyfluthrin	0.00028	0.00066	0.0028	**0.0038**	0.0013	0.00029	**0.0016**
DDT	21	0.22	6.0	**28**	0.42	54	**55**
Deltamethrin	5.3E-05	0.00017	0.0091	**0.0093**	0.00034	0.028	**0.028**
Etofenprox	0.13	4.4E-05	0.011	**0.14**	8.5E-05	0.034	**0.034**
Fenitrothion	4.7	16	3.1	**24**	30	12	**42**
Lambda-cyhalothrin	0.0059	0.0016	0.010	**0.018**	0.0031	0.031	**0.034**
Malathion	0.095	0.97	0.058	**1.1**	1.9	0.011	**1.9**
Pirimiphos-methyl	51	13	4.3	**68**	24	0.62	**25**
Propoxur	0.0036	0.97	0.60	**1.6**	1.9	10	**12**

Table C2-2a. Chronic Hazard Quotients:
Long-lasting Insecticidal Nets, Sleeping, Residents (Scenarios R-LLIN-1–13)

Product / Active Ingredient	Adult Dermal	Adult Inhalation	Adult Total	Child Dermal	Child Inhalation	Child Total
Alpha-cypermethrin (Interceptor G2)	0.16	0.0035	**0.17**	0.19	0.0072	**0.20**
Chlorfenapyr (Interceptor G2)	0.15	8.3E-05	**0.15**	0.18	0.00017	**0.18**
Interceptor G2 (Total)	**0.32**	**0.0036**	**0.32**	**0.37**	**0.0074**	**0.38**
Alpha-cypermethrin (Royal Guard)	0.37	0.0035	**0.37**	0.44	0.0072	**0.44**
Pyriproxyfen (Royal Guard)	0.025	1.2E-05	**0.025**	0.030	2.4E-05	**0.030**
Royal Guard (Total)	**0.40**	**0.0035**	**0.40**	**0.47**	**0.0073**	**0.47**
Alpha-cypermethrin (Royal Sentry)	0.43	0.0035	**0.43**	0.51	0.0072	**0.51**
Permethrin (Olyset Duo)	0.0063	2.4E-05	**0.0063**	0.0075	4.9E-05	**0.0075**

Product / Active Ingredient	Adult Dermal	Adult Inhalation	**Adult Total**	Child Dermal	Child Inhalation	**Child Total**
Pyriproxyfen (Olyset Duo)	0.045	1.2E-05	**0.045**	0.053	2.4E-05	**0.053**
Olyset Duo (Total)	**0.051**	**3.6E-05**	**0.051**	**0.061**	**7.3E-05**	**0.061**
Permethrin (Olyset Plus)	0.0063	2.4E-05	**0.0063**	0.0075	4.9E-05	**0.0075**
Piperonyl Butoxide (Olyset Plus)	NA	0.0018	**0.0018**	NA	0.0037	**0.0037**
Olyset Plus (Total)	**0.0063**	**0.0018**	**0.0081**	**0.0075**	**0.0037**	**0.011**
Deltamethrin (Panda Net 2.0)	3.0E-04	1.2E-05	**0.00031**	0.00035	2.4E-05	**0.00038**
Alpha-cypermethrin (DuraNet)	0.41	0.0035	**0.41**	0.48	0.0072	**0.49**
Deltamethrin (DawaPlus)	0.00034	1.2E-05	**0.00035**	4.0E-04	2.4E-05	**0.00042**
Deltamethrin (Permanet 3.0)	0.00034	1.2E-05	**0.00035**	4.0E-04	2.4E-05	**0.00042**
Piperonyl butoxide (Permanet 3.0)	NA	0.0018	**0.0018**	NA	0.0037	**0.0037**
Permanet 3.0 (Total)	**0.00034**	**0.0018**	**0.0021**	**4.0E-04**	**0.0037**	**0.0041**
Lambda cyhalothrin (ICON-MAXX)	0.020	0.00011	**0.020**	0.023	0.00022	**0.024**
Permethrin (Olyset)	0.0079	2.4E-05	**0.0079**	0.0093	4.9E-05	**0.0094**
Alpha-cypermethrin (ITN)	0.066	0.0035	**0.069**	0.078	0.0072	**0.085**
Cyfluthrin (ITN)	0.00066	4.5E-05	**7.0E-04**	0.00078	9.1E-05	**0.00087**
Deltamethrin (ITN)	9.9E-05	1.2E-05	**0.00011**	0.00012	2.4E-05	**0.00014**
Etofenprox (ITN)	0.21	3.0E-06	**0.21**	0.25	6.1E-06	**0.25**
Lambda cyhalothrin (ITN)	0.0059	0.00011	**0.0060**	0.0070	0.00022	**0.0072**
Permethrin (ITN)	0.0039	2.4E-05	**0.0040**	0.0047	4.9E-05	**0.0047**

Product / Active Ingredient	Toddler Dermal	Toddler Inhalation	Toddler Hand-mouth	Toddler Direct Oral	Toddler Total
Alpha-cypermethrin (Interceptor G2)	0.27	0.020	0.23	2.0	**2.5**
Chlorfenapyr (Interceptor G2)	0.25	0.00046	0.11	0.91	**1.3**
Interceptor G2 (Total)	**0.51**	**0.020**	**0.33**	**2.9**	**3.7**
Alpha-cypermethrin (Royal Guard)	0.60	0.020	0.51	4.4	**5.6**
Pyriproxyfen (Royal Guard)	0.041	6.7E-05	0.0088	0.076	**0.13**
Royal Guard (Total)	**0.64**	**0.020**	**0.52**	**4.5**	**5.7**

Product / Active Ingredient	Toddler Dermal	Toddler Inhalation	Toddler Hand-mouth	Toddler Direct Oral	Toddler Total
Alpha-cypermethrin (Royal Sentry)	0.69	0.020	0.60	5.1	**6.4**
Permethrin (Olyset Duo)	0.010	0.00013	0.044	0.38	**0.43**
Pyriproxyfen (Olyset Duo)	0.073	6.7E-05	0.016	0.13	**0.22**
Olyset Duo (Total)	**0.083**	**2.0E-04**	**0.060**	**0.51**	**0.65**
Permethrin (Olyset Plus)	0.010	0.00013	0.044	0.38	**0.43**
Piperonyl Butoxide (Olyset Plus)	NA	0.010	0.034	0.29	**0.34**
Olyset Plus (Total)	**0.010**	**0.010**	**0.078**	**0.67**	**0.77**
Deltamethrin (Panda Net 2.0)	0.00049	6.6E-05	0.21	1.8	**2.0**
Alpha-cypermethrin (DuraNet)	0.66	0.020	0.57	4.9	**6.1**
Deltamethrin (DawaPlus)	0.00054	6.6E-05	0.23	2.0	**2.2**
Deltamethrin (Permanet 3.0)	0.00054	6.6E-05	0.23	2.0	**2.2**
Piperonyl butoxide (Permanet 3.0)	NA	0.010	0.017	0.15	**0.17**
Permanet 3.0 (Total)	**0.00054**	**0.010**	**0.25**	**2.2**	**2.4**
Lambda cyhalothrin (ICON-MAXX)	0.032	0.00062	0.14	1.2	**1.3**
Permethrin (Olyset)	0.013	0.00013	0.055	0.47	**0.54**
Alpha-cypermethrin (ITN)	0.11	0.020	0.091	0.79	**1.0**
Cyfluthrin (ITN)	0.0011	0.00025	0.027	0.24	**0.26**
Deltamethrin (ITN)	0.00016	6.6E-05	0.069	0.59	**0.66**
Etofenprox (ITN)	0.35	1.7E-05	0.074	0.64	**1.1**
Lambda cyhalothrin (ITN)	0.0096	0.00062	0.041	0.35	**0.4**
Permethrin (ITN)	0.0064	0.00013	0.027	0.24	**0.27**

Product / Active Ingredient	Infant Dermal	Infant Inhalation	Infant Hand-mouth	Infant Direct Oral	Infant Breast Milk	Infant Total
Alpha-cypermethrin (Interceptor G2)	0.36	0.050	0.31	5.7	0.22	**6.7**
Chlorfenapyr (Interceptor G2)	0.33	0.0012	0.14	2.6	0.025	**3.1**
Interceptor G2 (Total)	**0.70**	**0.051**	**0.46**	**8.4**	**0.25**	**9.8**
Alpha-cypermethrin (Royal Guard)	0.82	0.050	0.70	13	0.49	**15**

Product / Active Ingredient	Infant Dermal	Infant Inhalation	Infant Hand-mouth	Infant Direct Oral	Infant Breast Milk	Infant Total
Pyriproxyfen (Royal Guard)	0.056	0.00017	0.012	0.22	0.054	**0.34**
Royal Guard (Total)	**0.87**	**0.050**	**0.72**	**13**	**0.54**	**15**
Alpha-cypermethrin (Royal Sentry)	0.95	0.050	0.82	15	0.57	**17**
Permethrin (Olyset Duo)	0.014	0.00034	0.060	1.1	0.009	**1.2**
Pyriproxyfen (Olyset Duo)	0.10	0.00017	0.021	0.39	0.097	**0.61**
Olyset Duo (Total)	**0.11**	**5.0E-04**	**0.081**	**1.5**	**0.11**	**1.8**
Permethrin (Olyset Plus)	0.014	0.00034	0.060	1.1	0.009	**1.2**
Piperonyl Butoxide (Olyset Plus)	NA	0.025	0.047	0.86	0.21	**1.1**
Olyset Plus (Total)	**0.014**	**0.025**	**0.11**	**2.0**	**0.22**	**2.3**
Deltamethrin (Panda Net 2.0)	0.00066	0.00017	0.29	5.2	1.3	**6.8**
Alpha-cypermethrin (DuraNet)	0.90	0.050	0.77	14	0.54	**16**
Deltamethrin (DawaPlus)	0.00074	0.00017	0.32	5.8	1.4	**7.6**
Deltamethrin (Permanet 3.0)	0.00074	0.00017	0.32	5.8	1.4	**7.6**
Piperonyl butoxide (Permanet 3.0)	NA	0.025	0.023	0.43	0.11	**0.58**
Permanet 3.0 (Total)	**0.00074**	**0.025**	**0.34**	**6.3**	**1.5**	**8.2**
Lambda cyhalothrin (ICON-MAXX)	0.044	0.0015	0.19	3.4	0.85	**4.5**
Permethrin (Olyset)	0.017	0.00034	0.075	1.4	0.011	**1.5**
Alpha-cypermethrin (ITN)	0.15	0.050	0.13	2.3	0.093	**2.7**
Cyfluthrin (ITN)	0.0015	0.00063	0.037	0.69	0.0056	**0.73**
Deltamethrin (ITN)	0.00022	0.00017	0.094	1.7	0.42	**2.2**
Etofenprox (ITN)	0.47	4.2E-05	0.10	1.9	0.46	**2.9**
Lambda cyhalothrin (ITN)	0.013	0.0015	0.056	1.0	0.25	**1.4**
Permethrin (ITN)	0.0087	0.00034	0.038	0.69	0.0056	**0.74**

Table C2-2b. Incremental Cancer Risk:
Long-lasting Insecticidal Nets, Sleeping, Residents (Scenarios R-LLIN-1–13)

Product / Active Ingredient	Adult Dermal	Adult Inhalation	**Adult Total**	Child Dermal	Child Inhalation	**Child Total**
Permethrin (Olyset Duo)	2.4E-04	2.0E-08	2.4E-04	3.6E-05	5.2E-09	**3.6E-05**
Permethrin (Olyset)	3.0E-04	2.0E-08	**3.0E-04**	4.5E-05	5.2E-09	**4.5E-05**
Permethrin (ITN)	**1.5E-04**	2.0E-08	**1.5E-04**	2.2E-05	5.2E-09	**2.2E-05**
Product / Active Ingredient	Toddler Dermal	Toddler Inhalation	Toddler Hand-mouth	Toddler Direct Oral	**Toddler Total**	
Permethrin (Olyset Duo)	4.9E-05	1.4E-08	1.1E-05	9.1E-05	**1.5E-04**	
Permethrin (Olyset)	6.1E-05	1.4E-08	1.3E-05	1.1E-04	**1.9E-04**	
Permethrin (ITN)	3.1E-05	1.4E-08	6.6E-06	5.7E-05	**9.4E-05**	
Product / Active Ingredient	Infant Dermal	Infant Inhalation	Infant Hand-mouth	Infant Direct Oral	Infant Breast Milk	**Infant Total**
Permethrin (Olyset Duo)	1.3E-05	7.1E-09	2.9E-06	5.3E-05	4.3E-07	**6.9E-05**
Permethrin (Olyset)	1.7E-05	7.1E-09	3.6E-06	6.6E-05	5.4E-07	**8.7E-05**
Permethrin (ITN)	8.4E-06	7.1E-09	1.8E-06	3.3E-05	2.7E-07	**4.3E-05**

Table C2-2c. Chronic Hazard Quotients:
Long-lasting Insecticidal Nets, Net Washing, Residents (Scenarios R-LLIN-14–18)

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	**Adult Total**	Child Dermal	Child Hand-mouth	**Child Total**	**Infant Breast Milk (only pathway)**
Alpha-cypermethrin (Interceptor G2)	0.0055	0.0057	**0.011**	0.0059	0.0064	**0.012**	**0.014**
Chlorfenapyr (Interceptor G2)	0.005	0.0026	**0.0077**	0.0055	0.0029	**0.0084**	**0.0013**
Interceptor G2 (Total)	**0.011**	**0.0083**	**0.019**	**0.011**	**0.0093**	**0.021**	**0.016**
Alpha-cypermethrin (Royal Guard)	0.012	0.013	**0.025**	0.013	0.014	**0.028**	**0.033**
Pyriproxyfen (Royal Guard)	0.00084	0.00022	**0.0011**	0.00092	0.00025	**0.0012**	**0.0023**
Royal Guard (Total)	**0.013**	**0.013**	**0.026**	**0.014**	**0.015**	**0.029**	**0.035**
Alpha-cypermethrin (Royal Sentry)	0.014	0.015	**0.029**	0.016	0.017	**0.032**	**0.038**

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	**Adult Total**	Child Dermal	Child Hand-mouth	**Child Total**	**Infant Breast Milk (only pathway)**
Permethrin (Olyset Duo)	0.00021	0.0011	**0.0013**	0.00023	0.0012	**0.0014**	**0.00038**
Pyriproxyfen (Olyset Duo)	0.0015	0.00039	**0.0019**	0.0016	0.00044	**0.0021**	**0.0040**
Olyset Duo (Total)	**0.0017**	**0.0015**	**0.0032**	**0.0019**	**0.0017**	**0.0035**	**0.0044**
Permethrin (Olyset Plus)	0.00021	0.0011	**0.0013**	0.00023	0.0012	**0.0014**	**0.00038**
Piperonyl Butoxide (Olyset Plus)	NA	0.00085	**0.00085**	NA	0.00095	**0.00095**	**0.0088**
Olyset Plus (Total)	**0.00021**	**0.0019**	**0.0021**	**0.00023**	**0.0022**	**0.0024**	**0.0092**
Deltamethrin (Panda Net 2.0)	1.0E-05	0.0052	**0.0052**	1.1E-05	0.0058	**0.0058**	**0.054**
Alpha-cypermethrin (DuraNet)	0.014	0.014	**0.028**	0.015	0.016	**0.030**	**0.036**
Deltamethrin (DawaPlus)	1.1E-05	0.0058	**0.0058**	1.2E-05	0.0065	**0.0065**	**0.060**
Deltamethrin (Permanet 3.0)	1.1E-05	0.0058	**0.0058**	1.2E-05	0.0065	**0.0065**	**0.060**
Piperonyl butoxide (Permanet 3.0)	NA	0.00042	**0.00042**	NA	0.00048	**0.00048**	**0.0044**
Permanet 3.0 (Total)	**1.1E-05**	**0.0062**	**0.0062**	**1.2E-05**	**0.0070**	**0.0070**	**0.065**
Lambda cyhalothrin (ICON-MAXX)	0.00066	0.0034	**0.0040**	0.00071	0.0038	**0.0045**	**0.035**
Permethrin (Olyset)	0.00026	0.0014	**0.0016**	0.00029	0.0015	**0.0018**	**0.00047**
Alpha-cypermethrin (ITN)	0.0022	0.0023	**0.0044**	0.0024	0.0025	**0.0049**	**0.0058**
Cyfluthrin (ITN)	2.2E-05	0.00068	**7.0E-04**	2.4E-05	0.00076	**0.00079**	**0.00024**
Deltamethrin (ITN)	3.3E-06	0.0017	**0.0017**	3.6E-06	0.0019	**0.0019**	**0.018**
Etofenprox (ITN)	0.0071	0.0018	**0.0089**	0.0077	0.0021	**0.0098**	**0.019**
Lambda cyhalothrin (ITN)	2.0E-04	0.0010	**0.0012**	0.00021	0.0011	**0.0014**	**0.011**
Permethrin (ITN)	0.00013	0.00068	**0.00081**	0.00014	0.00076	**0.00091**	**0.00024**

Table C2-2d. Incremental Cancer Risk:
Long-lasting Insecticidal Nets, Net Washing, Residents (Scenarios R-LLIN-14–18)

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	**Adult Total**	Child Dermal	Child Hand-mouth	**Child Total**	**Infant Breast Milk (only pathway)**
Permethrin (Olyset Duo)	2.0E-07	5.2E-08	**2.5E-07**	2.2E-07	5.9E-08	**2.8E-07**	**1.8E-08**
Permethrin (Olyset)	2.5E-07	6.5E-08	**3.2E-07**	2.7E-07	7.3E-08	**3.5E-07**	**2.3E-08**
Permethrin (ITN)	1.3E-07	3.3E-08	**1.6E-07**	1.4E-07	3.7E-08	**1.7E-07**	**1.1E-08**

Table C2-2e Acute Hazard Quotients:
Long-lasting Insecticidal Nets, Net Washing, Residents (Scenarios R-LLIN-19–22)

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	**Adult Total**	Child Dermal	Child Hand-mouth	**Child Total**
Alpha-cypermethrin (Interceptor G2)	0.0014	0.019	**0.020**	0.0016	0.021	**0.022**
Chlorfenapyr (Interceptor G2)	0.014	0.0082	**0.023**	0.016	0.0093	**0.025**
Interceptor G2 (Total)	**0.016**	**0.027**	**0.043**	**0.017**	**0.030**	**0.047**
Alpha-cypermethrin (Royal Guard)	0.0032	0.042	**0.045**	0.0035	0.047	**0.051**
Pyriproxyfen (Royal Guard)	NA	0.0042	**0.0042**	NA	0.0047	**0.0047**
Royal Guard (Total)	**0.0032**	**0.046**	**0.049**	**0.0035**	**0.052**	**0.055**
Alpha-cypermethrin (Royal Sentry)	0.0038	0.048	**0.052**	0.0041	0.055	**0.059**
Permethrin (Olyset Duo)	0.011	0.059	**0.071**	0.012	0.067	**0.079**
Pyriproxyfen (Olyset Duo)	NA	0.0074	**0.0074**	NA	0.0084	**0.0084**
Olyset Duo (Total)	**0.011**	**0.067**	**0.078**	**0.012**	**0.075**	**0.088**
Permethrin (Olyset Plus)	0.011	0.059	**0.071**	0.012	0.067	**0.079**
Piperonyl Butoxide (Olyset Plus)	NA	0.0083	**0.0083**	NA	0.0094	**0.0094**
Olyset Plus (Total)	**0.011**	**0.068**	**0.079**	**0.012**	**0.076**	**0.089**
Deltamethrin (Panda Net 2.0)	0.00055	0.28	**0.28**	0.00059	0.32	**0.32**
Alpha-cypermethrin (DuraNet)	0.0036	0.046	**0.049**	0.0039	0.052	**0.056**
Deltamethrin (DawaPlus)	0.00061	0.32	**0.32**	0.00066	0.36	**0.36**
Deltamethrin (Permanet 3.0)	0.00061	0.32	**0.32**	0.00066	0.36	**0.36**
Piperonyl butoxide (Permanet 3.0)	NA	0.0042	**0.0042**	NA	0.0047	**0.0047**

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	**Adult Total**	Child Dermal	Child Hand-mouth	**Child Total**
Permanet 3.0 (Total)	**0.00061**	**0.32**	**0.32**	**0.00066**	**0.36**	**0.36**
Lambda cyhalothrin (ICON-MAXX)	0.036	0.19	**0.22**	0.039	0.21	**0.25**
Permethrin (Olyset)	0.014	0.074	**0.089**	0.016	0.084	**0.099**
Alpha-cypermethrin (ITN)	0.00057	0.0074	**0.008**	0.00062	0.0084	**0.009**
Cyfluthrin (ITN)	0.0012	0.037	**0.038**	0.0013	0.042	**0.043**
Deltamethrin (ITN)	0.00018	0.093	**0.093**	2.0E-04	0.10	**0.10**
Etofenprox (ITN)	0.036	0.10	**0.14**	0.039	0.11	**0.15**
Lambda cyhalothrin (ITN)	0.011	0.056	**0.066**	0.012	0.063	**0.074**
Permethrin (ITN)	0.0072	0.037	**0.044**	0.0078	0.042	**0.050**

Table C2-3a. Chronic Hazard Quotients:
Larvicides, Mixing/Loading and Spraying, Worker (Scenarios W-Larv-1–4)

Product / Active Ingredient	Worker Mixing/Loading Dermal With PPE	Worker Spraying Dermal With PPE	**Worker Total With PPE**	Worker Mixing/Loading Dermal No PPE	Worker Spraying Dermal No PPE	**Worker Total No PPE**
Chlorpyrifos	2.7E-07	7.9E-06	**8.2E-06**	9.1E-06	0.00034	**0.00035**
Diflubenzuron (DT)	2.5E-09	2.8E-06	**2.8E-06**	1.3E-07	0.00012	**0.00012**
Diflubenzuron (G)	2.5E-09	2.8E-06	**2.8E-06**	1.3E-07	0.00012	**0.00012**
Diflubenzuron (WP)	1.1E-06	2.8E-06	**3.9E-06**	5.5E-05	0.00012	**0.00018**
Fenthion	0.00019	0.0055	**0.0056**	0.0063	0.24	**0.24**
Methoprene	1.2E-08	3.4E-07	**3.5E-07**	3.9E-07	1.5E-05	**1.5E-05**
Novaluron	3.6E-06	1.0E-04	**0.00011**	0.00012	0.0045	**0.0046**
Pirimiphos-methyl	0.00028	0.0081	**0.0084**	0.0094	0.35	**0.36**
Pyriproxyfen	5.6E-08	1.6E-06	**1.7E-06**	1.9E-06	7.1E-05	**7.3E-05**
Spinosad (all formulations)	NA	NA	**NA**	NA	NA	**NA**
Temephos (EC)	5.6E-05	0.0016	**0.0017**	0.0019	0.070	**0.072**
Temephos (G)	1.4E-06	0.0016	**0.0016**	7.1E-05	0.070	**0.070**

Table C2-3b. Chronic Hazard Quotients:
Larvicides, Ground Water Exposures, Residents (Scenarios R-Larv-1–8)

Product / Active Ingredient	Adult Ground Water Ingestion	Adult Ground Water Dermal	**Adult Total**	Child Ground Water Ingestion	Child Ground Water Dermal	**Child Total**
Chlorpyrifos	0.00014	2.6E-08	**0.00014**	0.00014	3.3E-08	**0.00014**
Diflubenzuron	2.3E-05	9.8E-09	**2.3E-05**	2.3E-05	1.2E-08	**2.3E-05**
Fenthion	0.022	5.6E-05	**0.022**	0.021	6.9E-05	**0.021**
Methoprene	3.4E-07	1.1E-09	**3.4E-07**	3.3E-07	1.4E-09	**3.3E-07**
Novaluron	4.3E-05	3.6E-07	**4.3E-05**	4.2E-05	4.5E-07	**4.2E-05**
Pirimiphos-methyl	0.0026	2.2E-05	**0.0027**	0.0025	2.8E-05	**0.0026**
Pyriproxyfen	6.4E-07	5.4E-09	**6.5E-07**	6.2E-07	6.7E-09	**6.3E-07**
Spinosad	8.3E-05	NA	**8.3E-05**	8.1E-05	NA	**8.1E-05**
Spinosad 83.3 Monolayer	8.3E-05	NA	**8.3E-05**	8.1E-05	NA	**8.1E-05**
Spinosad 25 Extended Release	6.7E-05	NA	**6.7E-05**	6.4E-05	NA	**6.4E-05**
Temephos	0.00017	5.4E-06	**0.00017**	0.00016	6.7E-06	**0.00017**

Product / Active Ingredient	Toddler Ground Water Ingestion	Toddler Ground Water Dermal	**Toddler Total**	Infant Ground Water Dermal	Infant Breast Milk	**Infant Total**
Chlorpyrifos	0.00032	4.2E-08	**0.00032**	5.8E-08	0.00031	**0.00031**
Diflubenzuron	5.2E-05	1.6E-08	**5.2E-05**	2.2E-08	5.0E-05	**5.0E-05**
Fenthion	0.049	8.9E-05	**0.049**	0.00012	0.047	**0.047**
Methoprene	7.5E-07	1.8E-09	**7.5E-07**	2.5E-09	7.3E-07	**7.3E-07**
Novaluron	9.5E-05	5.8E-07	**9.6E-05**	8.1E-07	9.3E-05	**9.4E-05**
Pirimiphos-methyl	0.0058	3.6E-05	**0.0059**	4.9E-05	0.00019	**0.00024**
Pyriproxyfen	1.4E-06	8.7E-09	**1.4E-06**	1.2E-08	1.4E-06	**1.4E-06**
Spinosad	0.00018	NA	**0.00018**	NA	1.2E-05	**1.2E-05**
Spinosad 83.3 Monolayer	0.00018	NA	**0.00018**	NA	1.2E-05	**1.2E-05**
Spinosad 25 Extended Release	0.00015	NA	**0.00015**	NA	9.6E-06	**9.6E-06**
Temephos	0.00037	8.6E-06	**0.00038**	1.2E-05	0.00037	**0.00038**

Table C2-3c. Incremental Cancer Risk:
Larvicides, Ground Water Exposures, Residents (Scenarios R-Larv-1–8)

Product / Active Ingredient	Adult Ground Water Ingestion	Adult Ground Water Dermal	**Adult Total**	Child Ground Water Ingestion	Child Ground Water Dermal	**Child Total**
Diflubenzuron; 4-chlorophenylurea metabolite	3.9E-09	3.30E-11	**3.9E-09**	4.80E-10	5.20E-12	**4.80E-10**
Product / Active Ingredient	Toddler Ground Water Ingestion	Toddler Ground Water Dermal	**Toddler Total**	Infant Ground Water Dermal	Infant Breast Milk	**Infant Total**
Diflubenzuron; 4-chlorophenylurea metabolite	1.1E-09	6.70E-12	**1.1E-09**	1.80E-12	2.10E-10	**2.20E-10**

Table C2-4a. Chronic Hazard Quotients:
Treated Hammocks, Sleeping, Residents (Scenarios R-Hamm-1–9)

Product / Active Ingredient	**Adult Dermal (only pathway)**	**Child Dermal (only pathway)**	Toddler Dermal	Toddler Hand-mouth	Toddler Direct Oral	**Toddler Total**
Permethrin	**0.025**	**0.030**	0.039	0.082	0.71	**0.83**
Deltamethrin	**0.00065**	**0.00081**	0.0010	0.22	1.9	**2.1**
Product / Active Ingredient	Infant Dermal	Infant Hand-mouth	Infant Direct Oral	Infant Breast Milk	**Infant Total**	
Permethrin	0.054	0.11	2.1	0.035	**2.3**	
Deltamethrin	0.0015	0.30	5.5	2.8	**8.6**	

Table C2-4b. Incremental Cancer Risk:
Treated Hammocks, Sleeping, Residents (Scenarios R-Hamm-1–9)

Product / Active Ingredient	**Adult Dermal (only pathway)**	**Child Dermal (only pathway)**	Toddler Dermal	Toddler Hand-mouth	Toddler Direct Oral	**Toddler Total**
Permethrin	**9.2E-04**	**1.5E-04**	1.9E-04	2.0E-05	1.7E-04	**3.8E-04**
Product / Active Ingredient	Infant Dermal	Infant Hand-mouth	Infant Direct Oral	Infant Breast Milk	**Infant Total**	
Permethrin	5.2E-05	5.4E-06	9.9E-05	1.7E-06	**1.6E-04**	

Table C2-4c. Chronic Hazard Quotients:
Treated Hammocks, Washing, Residents (Scenarios R-Hamm-10-14)

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	**Adult Total**	Child Dermal	Child Hand-mouth	**Child Total**	**Infant Breast Milk (only pathway)**
Permethrin	5.6E-05	0.00029	**0.00034**	6.1E-05	0.00032	0.00039	**0.00010**
Deltamethrin	1.5E-06	0.00077	**0.00077**	1.6E-06	0.00087	0.00087	**0.0080**

Table C2-4d. Incremental Cancer Risk:
Treated Hammocks, Washing, Residents (Scenarios R-Hamm-10-14)

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	**Adult Total**	Child Dermal	Child Hand-mouth	**Child Total**	**Infant Breast Milk (only pathway)**
Permethrin	5.4E-08	1.4E-08	**6.8E-08**	5.8E-08	1.6E-08	**7.4E-08**	**4.8E-09**

Table C2-4e. Acute Hazard Quotients:
Treated Hammocks, Washing, Residents (Scenarios R-Hamm-15-18)

Product / Active Ingredient	Adult Dermal	Adult Hand-mouth	**Adult Total**	Child Dermal	Child Hand-mouth	**Child Total**
Permethrin	0.0031	0.016	**0.019**	0.0033	0.018	**0.021**
Deltamethrin	8.2E-05	0.042	**0.042**	8.9E-05	0.047	**0.048**

ANNEX C3: AGGREGATE HAZARD QUOTIENT FIGURES FOR ALL INSECTICIDES

Figure C3-1a. Aggregate HQs - IRS - All Insecticides - Chronic Exposure for Workers

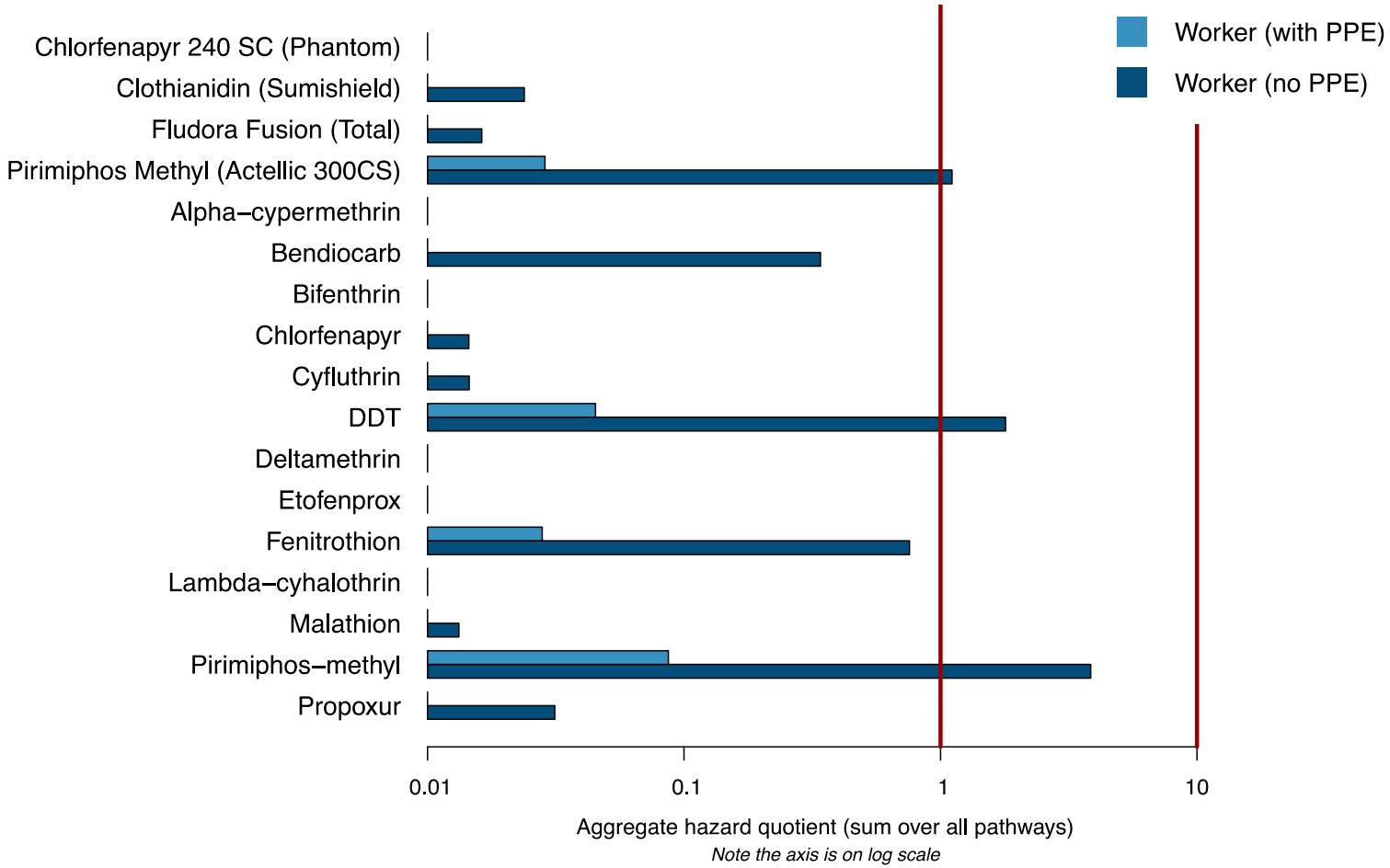


Figure C3-1b. Aggregate HQs - IRS - All Insecticides - Chronic Exposure for Residents

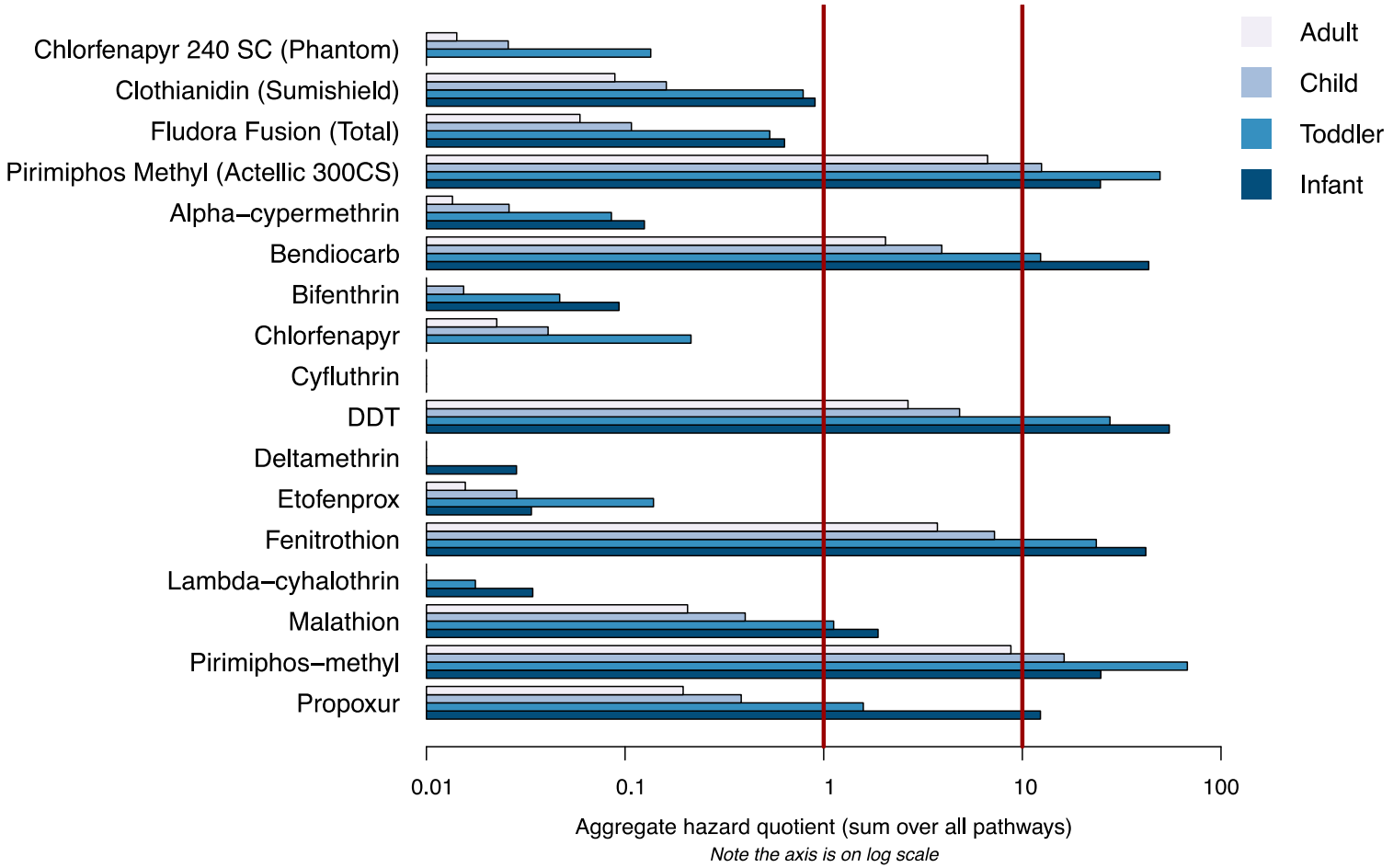


Figure C3-2. Aggregate HQs - LLIN - All Insecticides - Chronic Exposure for Residents

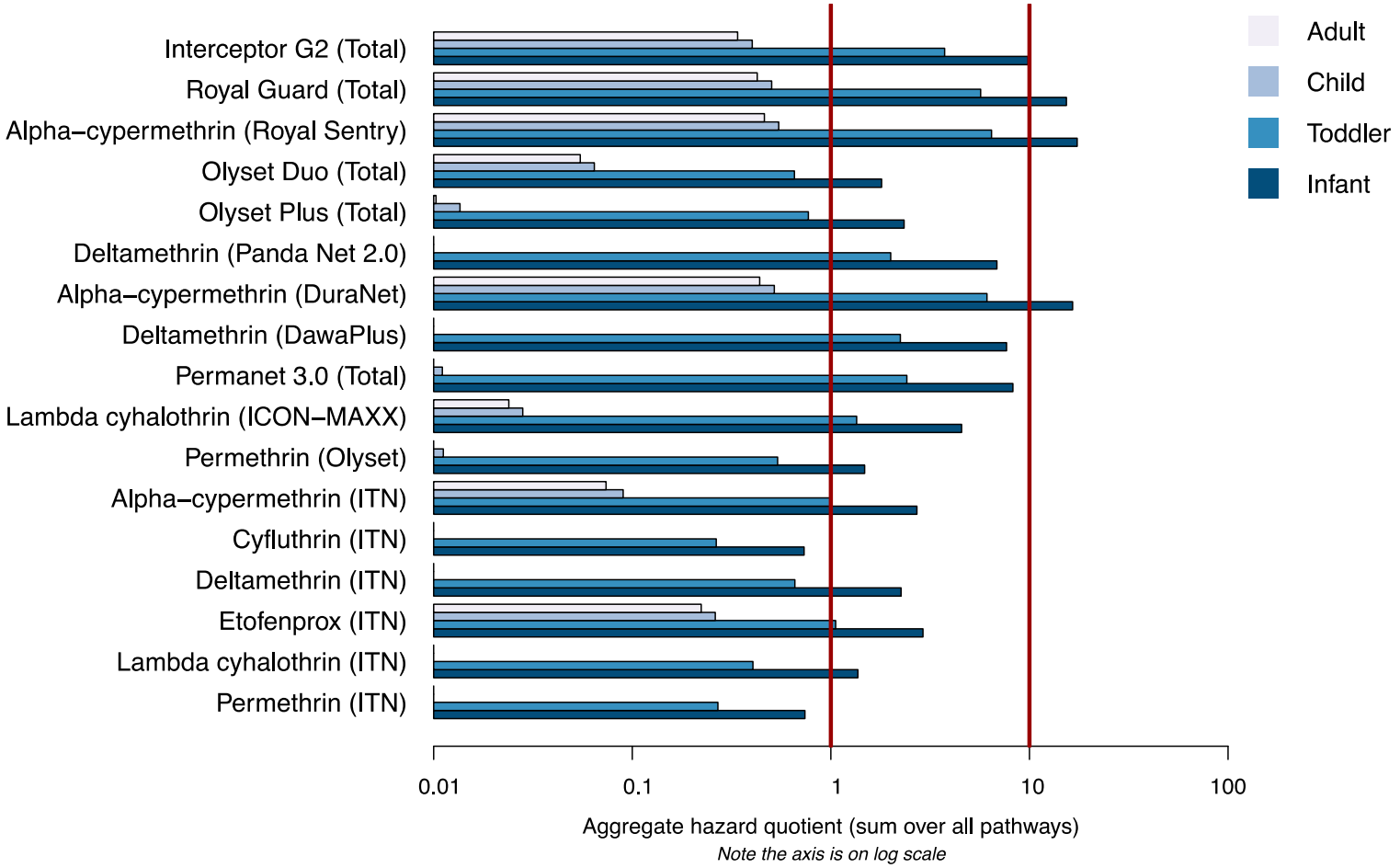


Figure C3-3a. Aggregate HQs - Larvicides - All Insecticides - Chronic Exposure for Workers

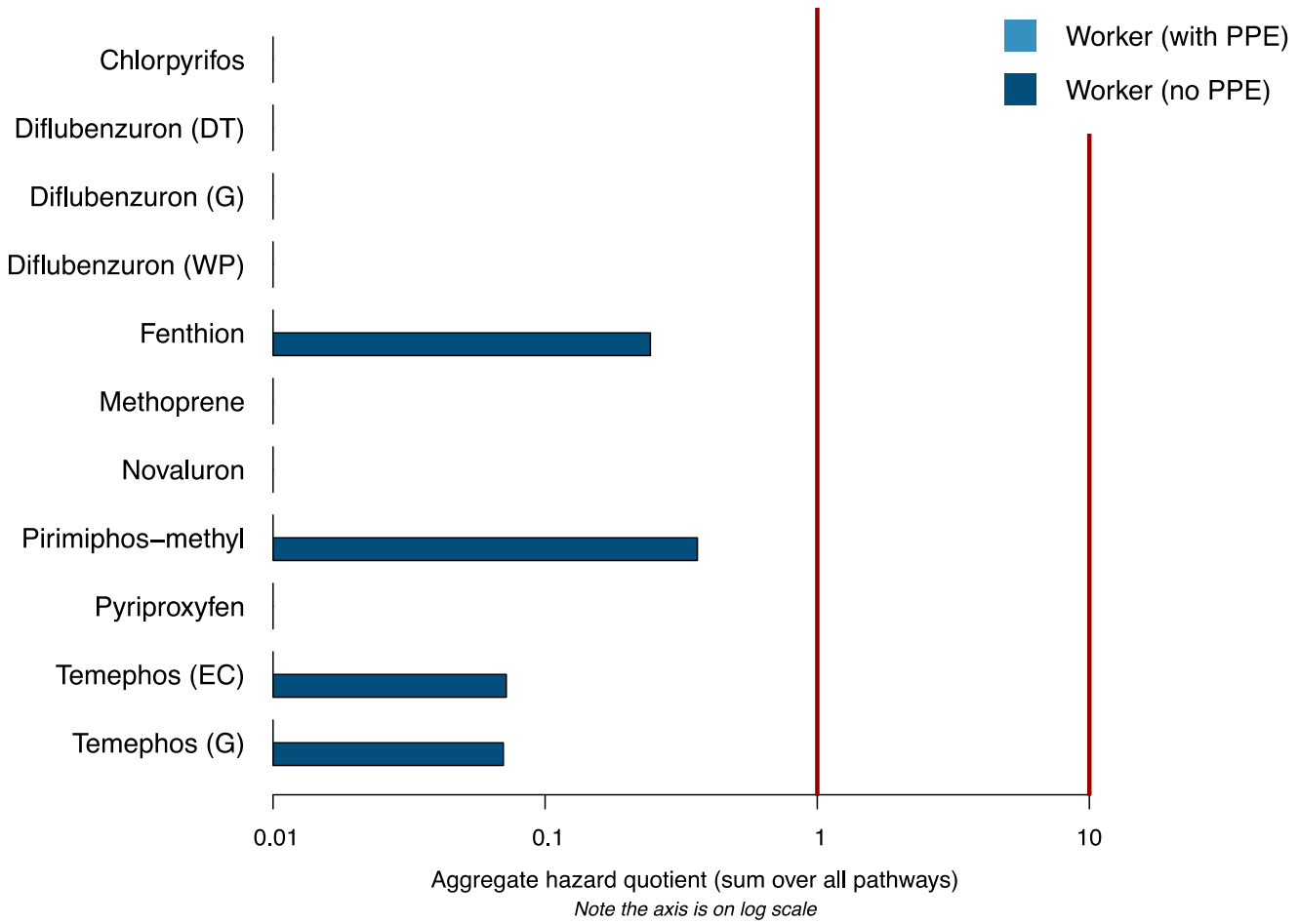


Figure C3-3b. Aggregate HQs - Larvicides - All Insecticides - Chronic Exposure for Residents

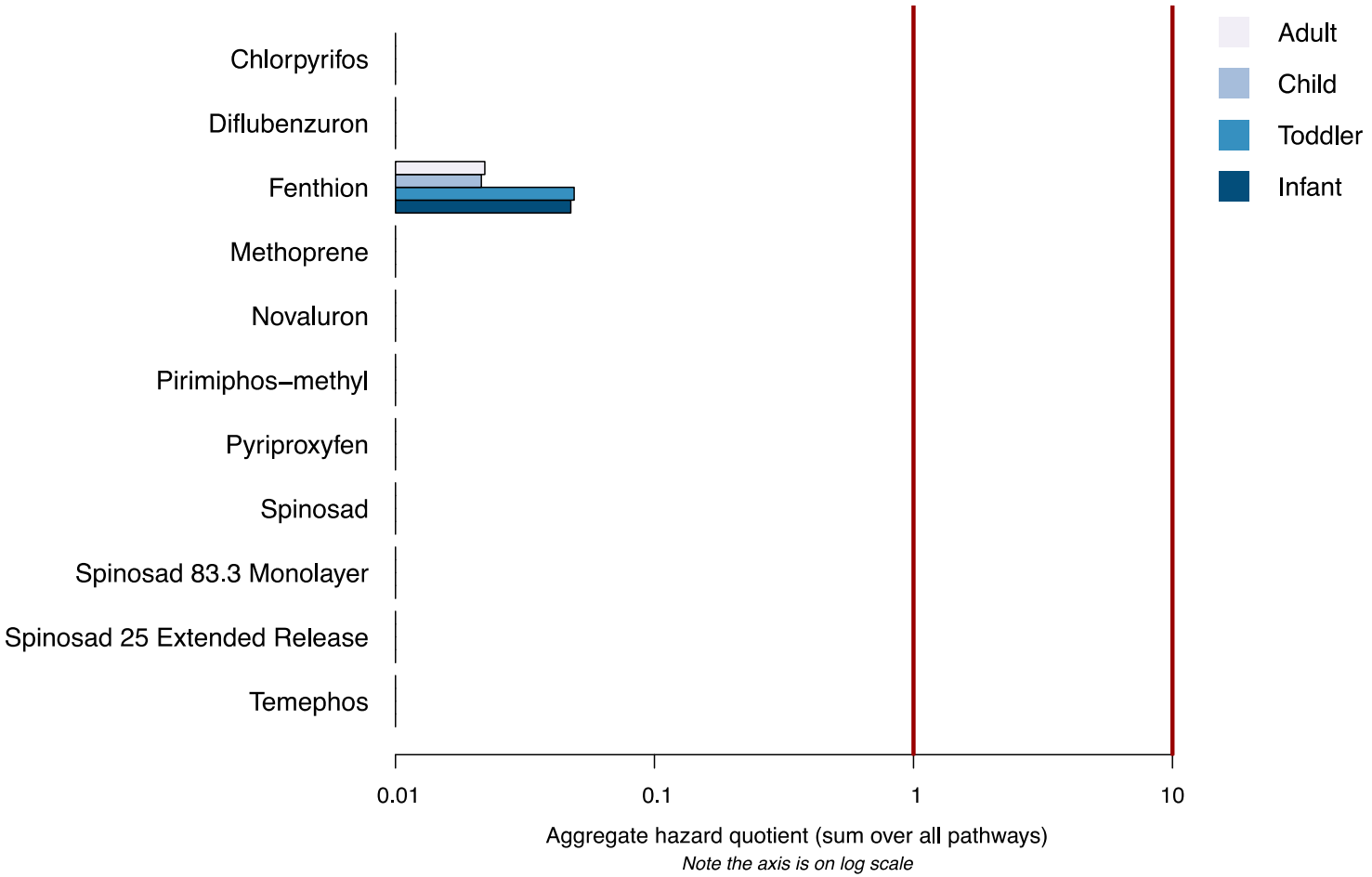
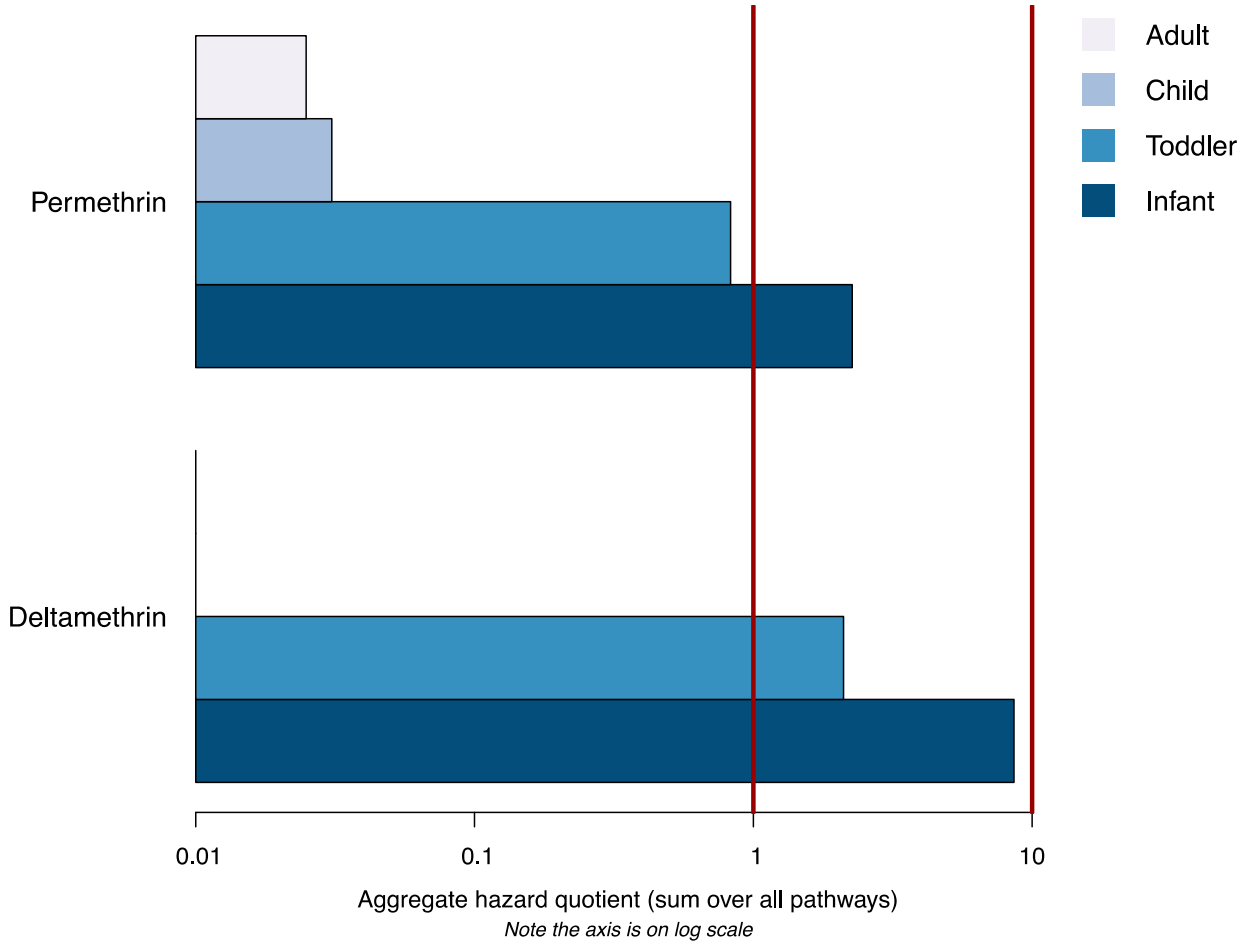
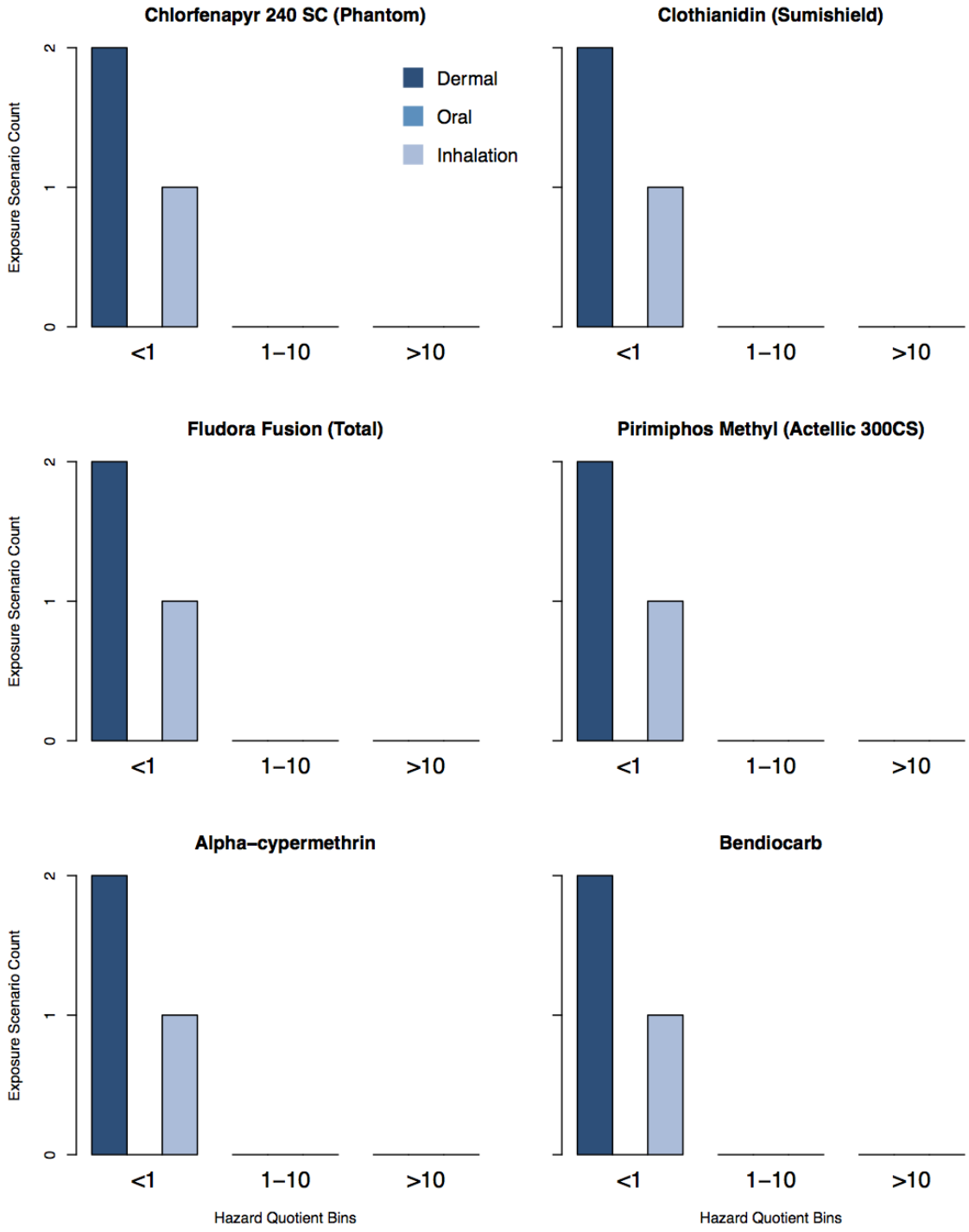


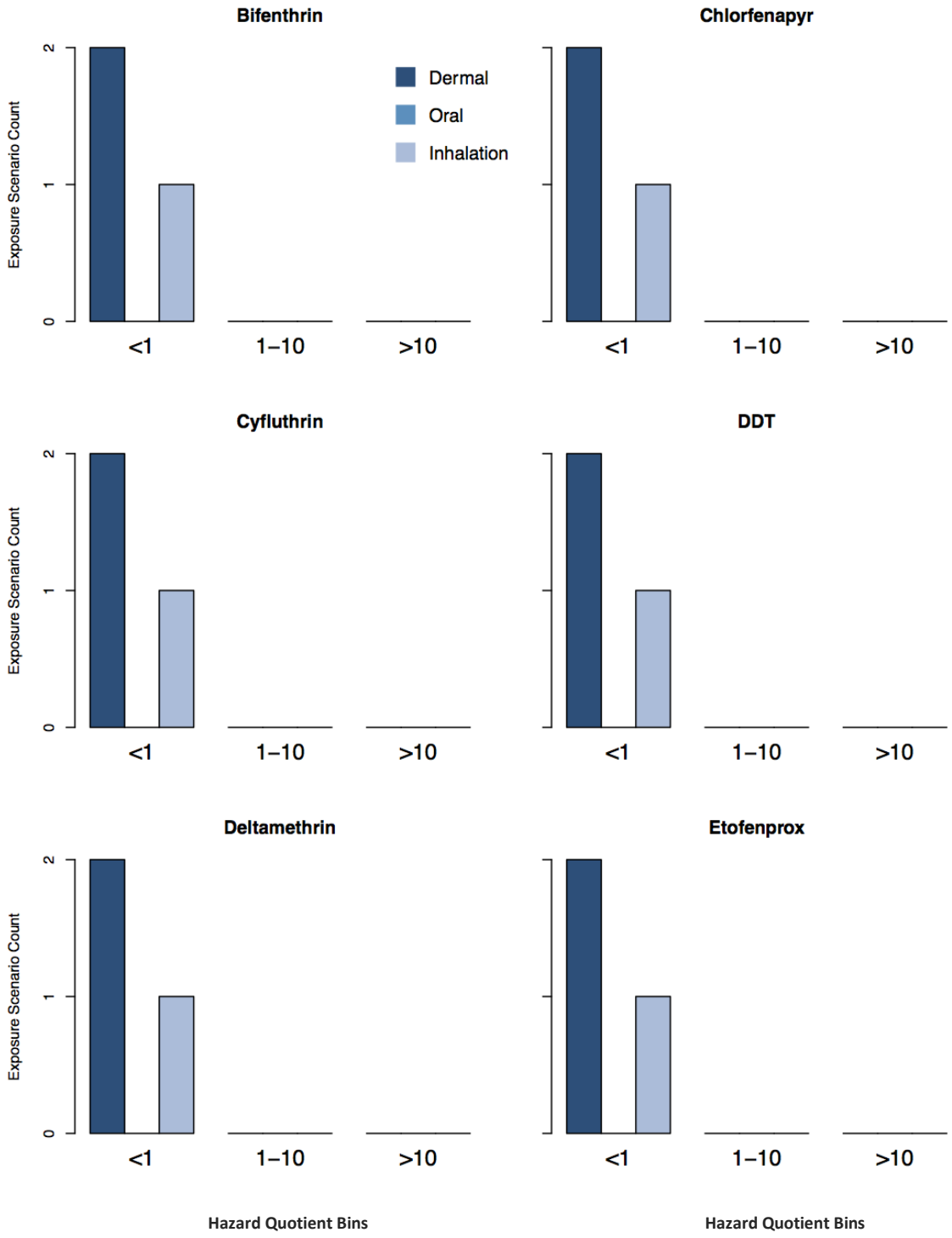
Figure C3-4. Aggregate HQs - Hammocks - All Insecticides - Chronic Exposure for Residents



ANNEX C4: RISK PROFILES FOR ALL INSECTICIDES

Figure C4-1a. Risk Profiles - IRS - All Insecticides - Worker Receptors




Bifenthrin
Chlorfenapyr
Cyfluthrin
DDT
Deltamethrin
Etofenprox
Dermal
Oral
Inhalation
Exposure Scenario Count
0
1
2
<1
1–10
>10
Hazard Quotient Bins

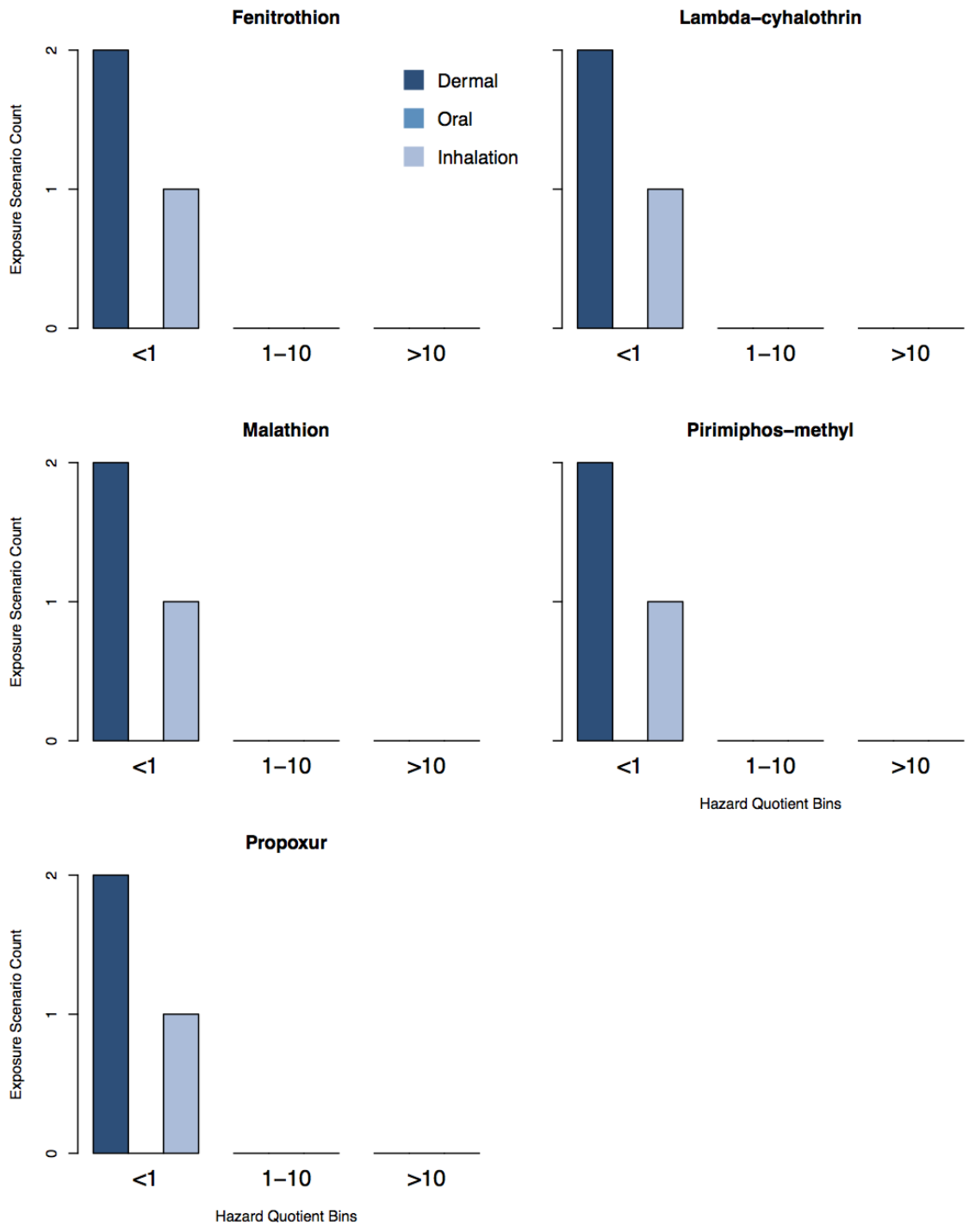
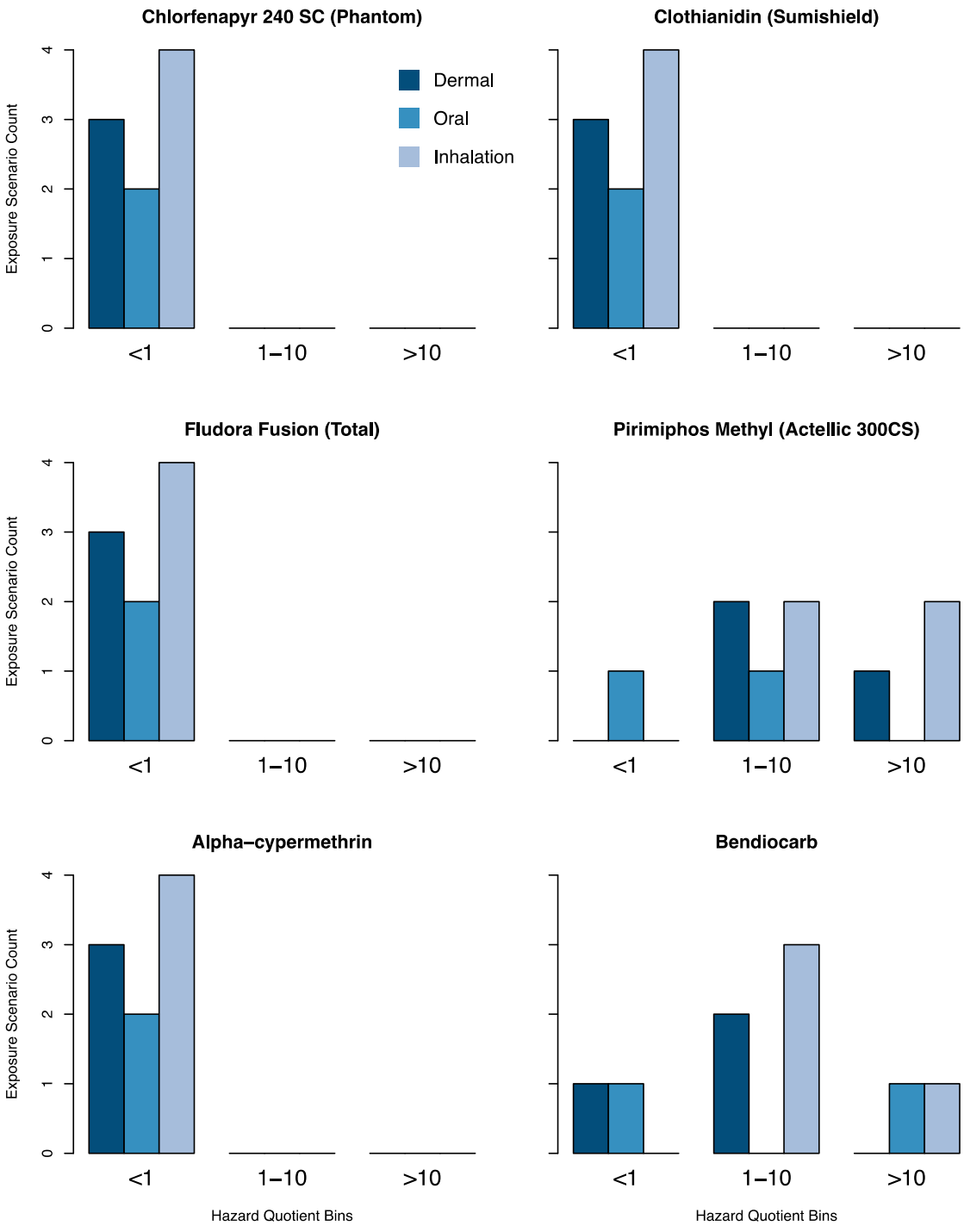
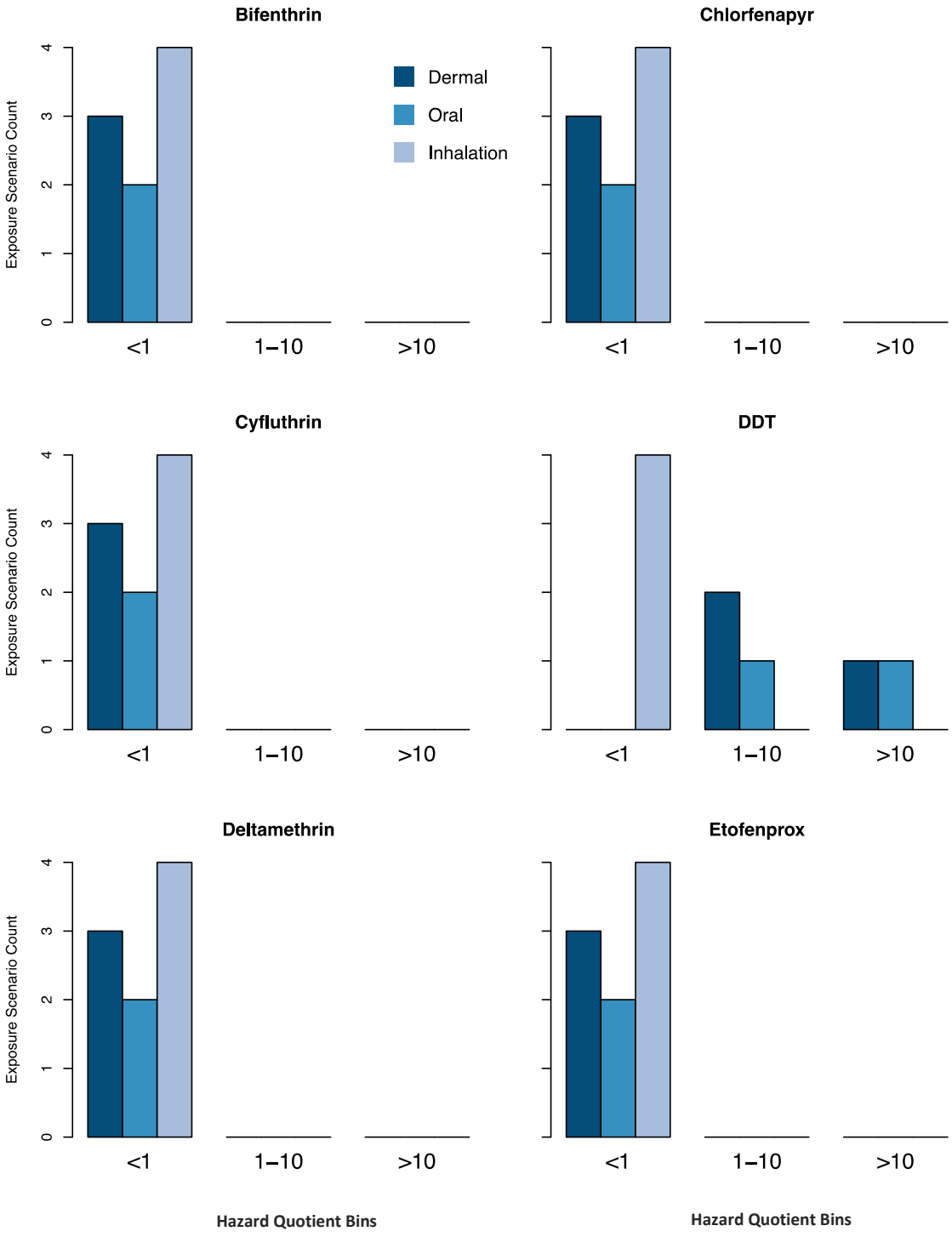

Fenitrothion
Lambda−cyhalothrin
Malathion
Pirimiphos−methyl
Propoxur
Dermal
Oral
Inhalation
Exposure Scenario Count
0
1
2
<1
1−10
>10
Hazard Quotient Bins

Figure C4-1b. Risk Profiles - IRS - All Insecticides - Resident Receptors




Bifenthrin
Chlorfenapyr
Cyfluthrin
DDT
Deltamethrin
Etofenprox
Dermal
Oral
Inhalation
Exposure Scenario Count
0
1
2
3
4
<1
1–10
>10
Hazard Quotient Bins

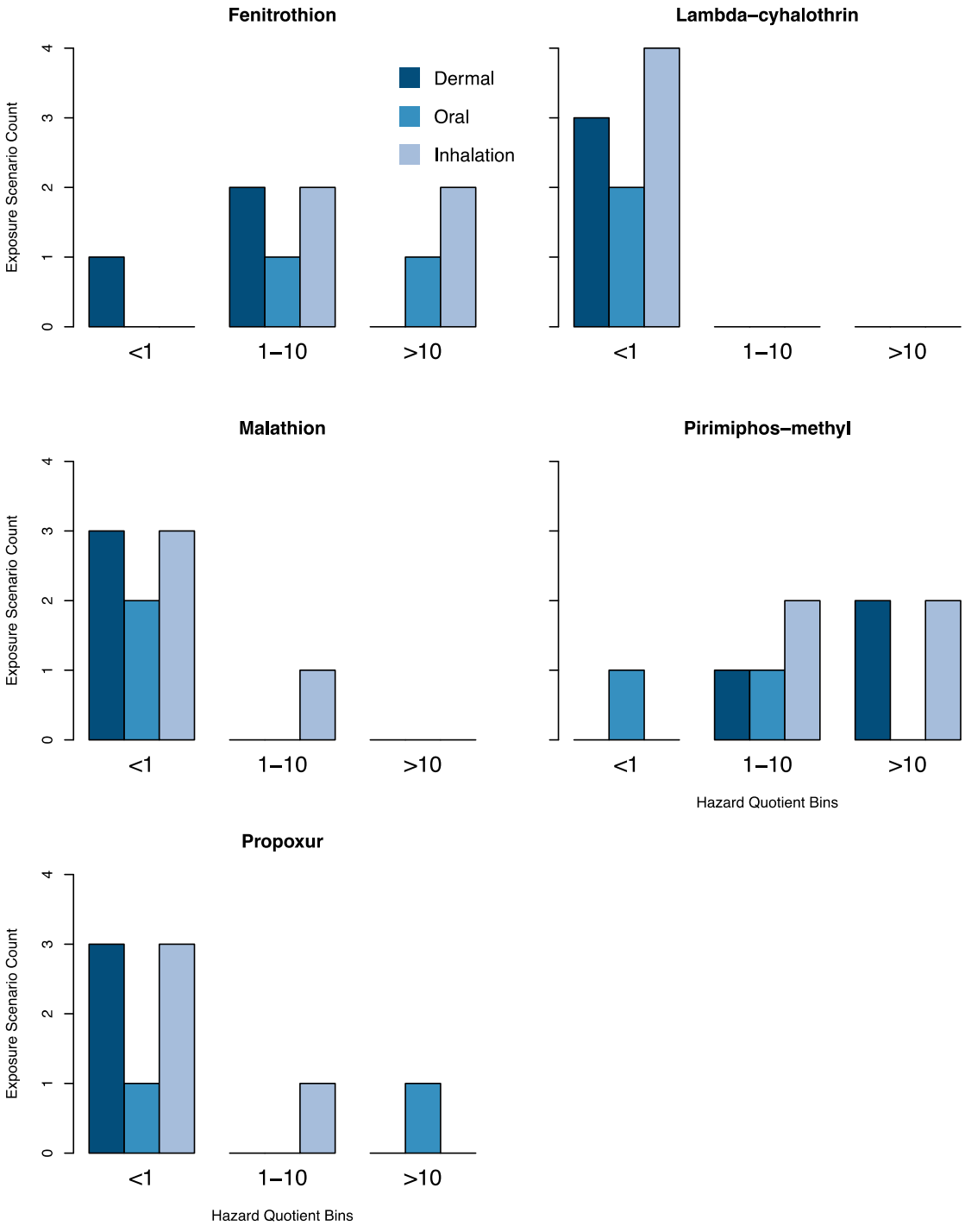
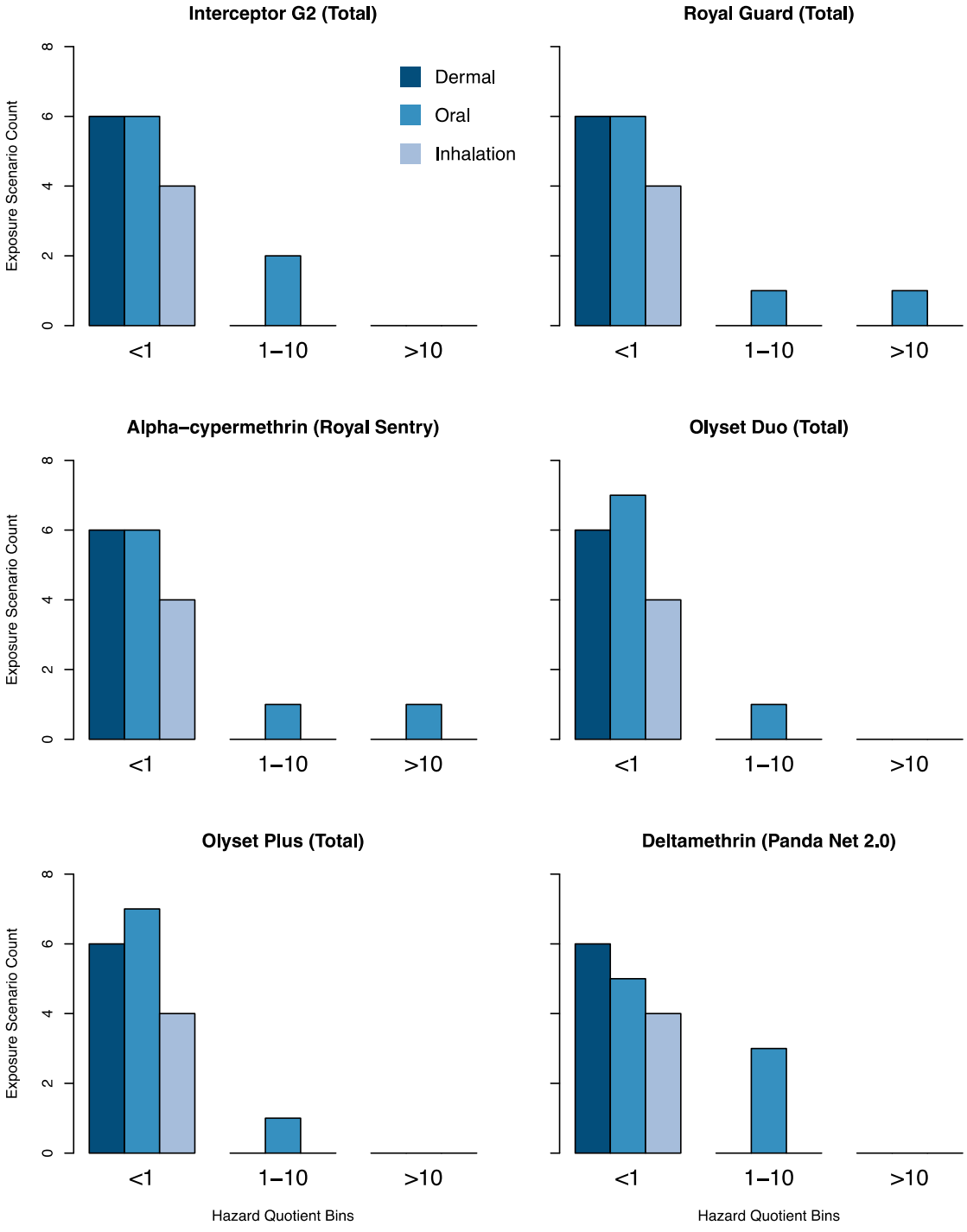
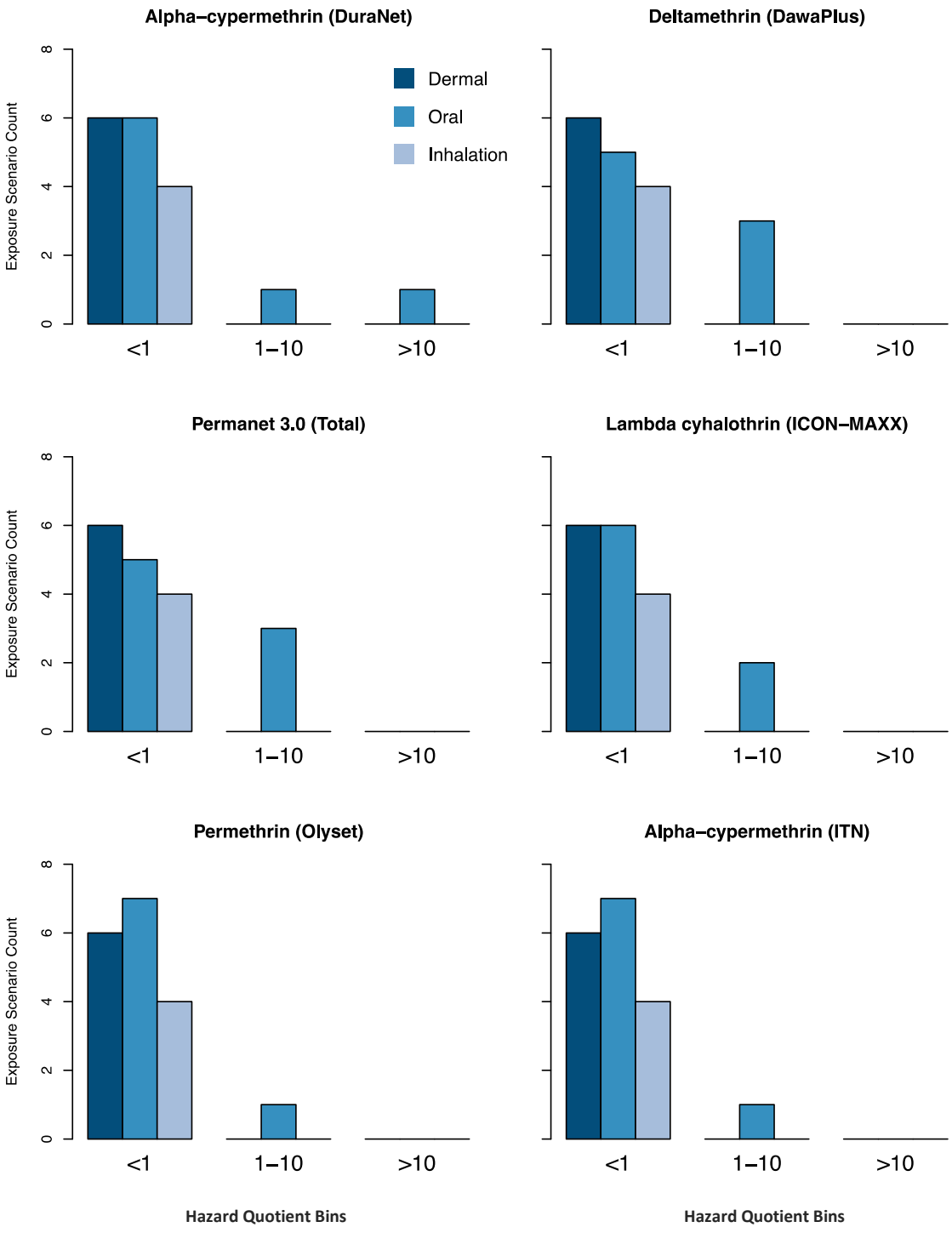

Fenitrothion
Lambda−cyhalothrin
Malathion
Pirimiphos−methyl
Propoxur
Dermal
Oral
Inhalation
Exposure Scenario Count
0
1
2
3
4
<1
1−10
>10
Hazard Quotient Bins

Figure C4-2. Risk Profiles - LLIN - All Insecticides - Resident Receptors




Alpha–cypermethrin (DuraNet)
Deltamethrin (DawaPlus)
Permanet 3.0 (Total)
Lambda cyhalothrin (ICON–MAXX)
Permethrin (Olyset)
Alpha–cypermethrin (ITN)
Dermal
Oral
Inhalation
Exposure Scenario Count
0
2
4
6
8
<1
1–10
>10
Hazard Quotient Bins

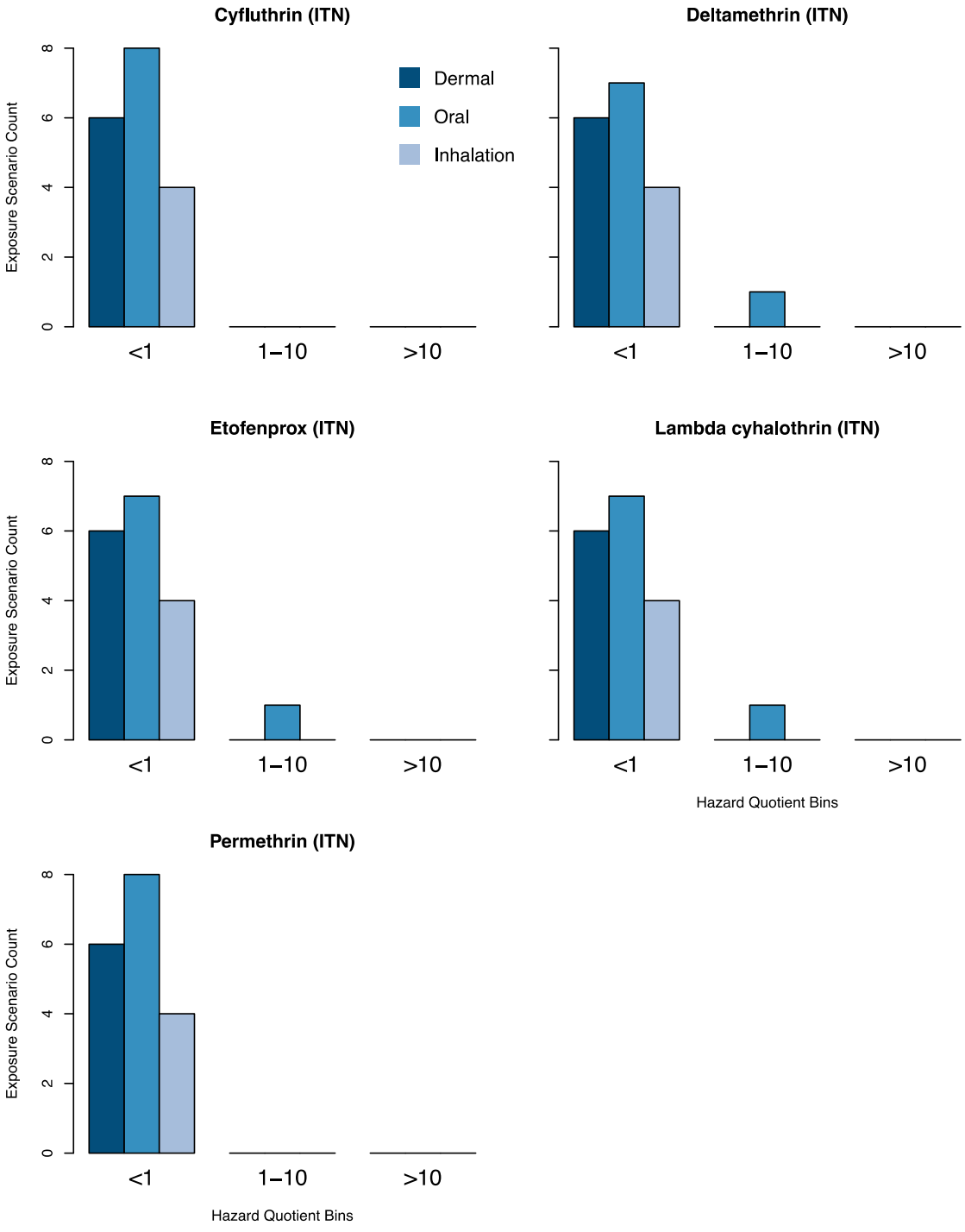
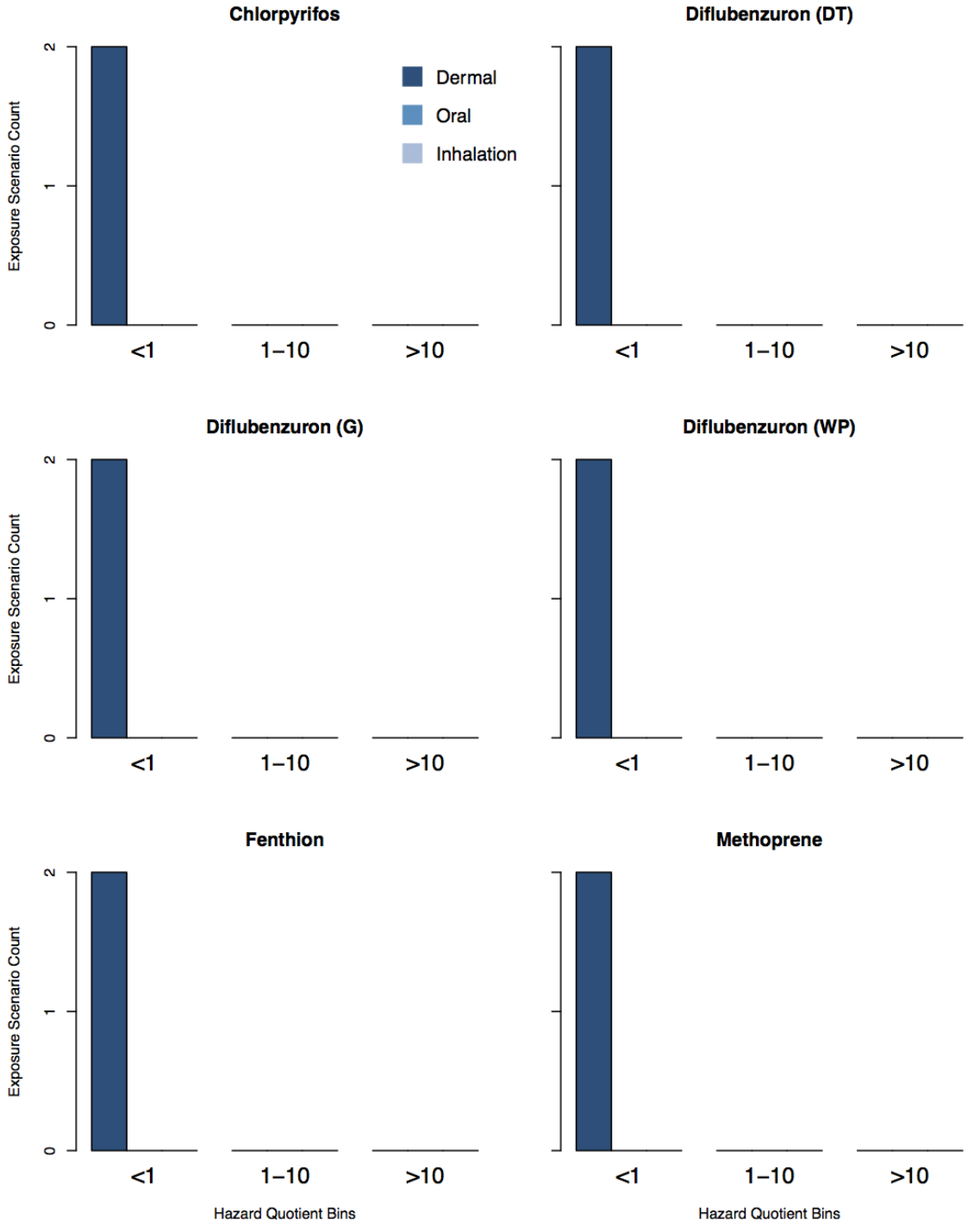

Cyfluthrin (ITN)
Deltamethrin (ITN)
Etofenprox (ITN)
Lambda cyhalothrin (ITN)
Permethrin (ITN)
Dermal
Oral
Inhalation
Exposure Scenario Count
0
2
4
6
8
<1
1–10
>10
Hazard Quotient Bins

Figure C4-3a. Risk Profiles - Larvicides - All Insecticides - Worker Receptors



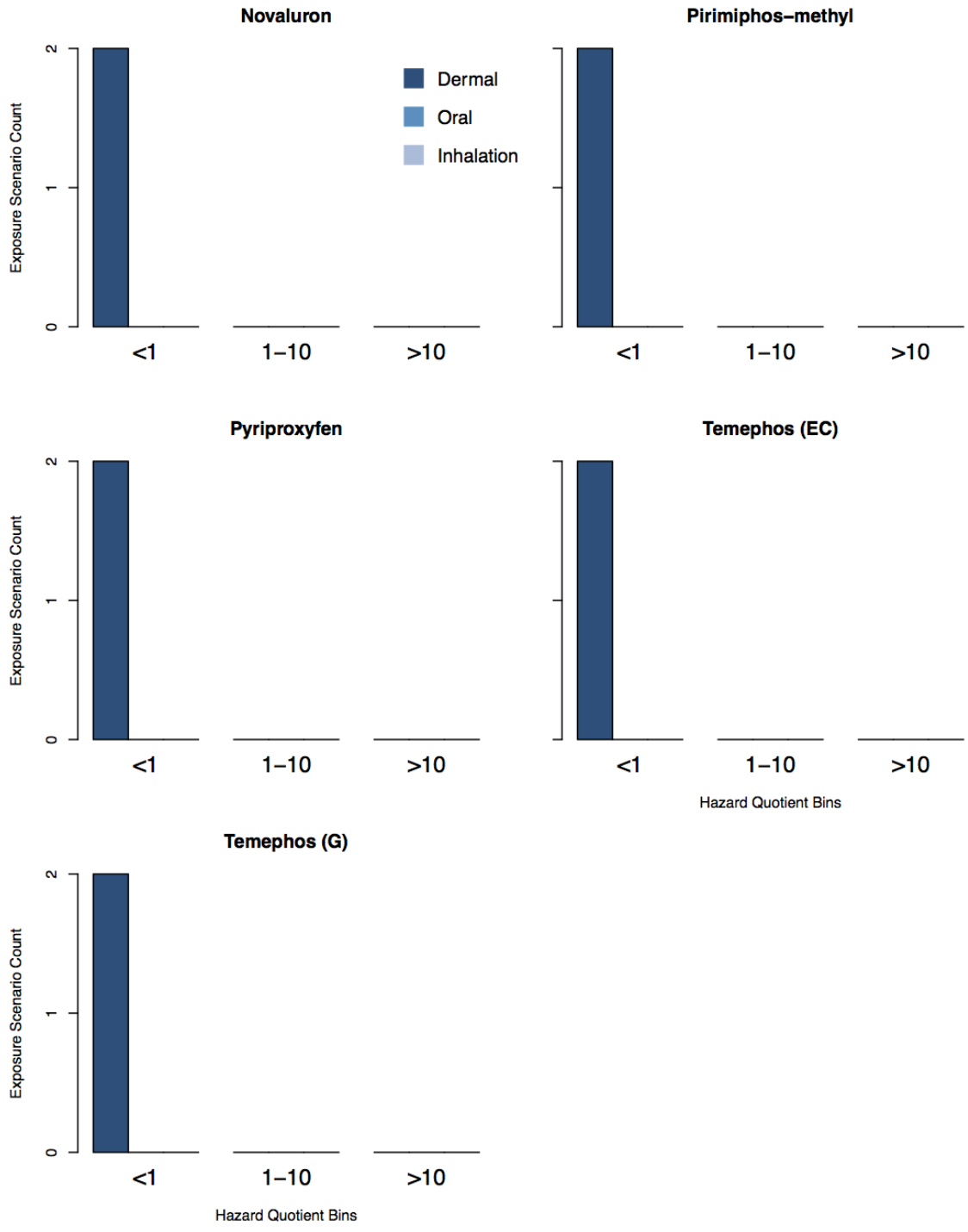
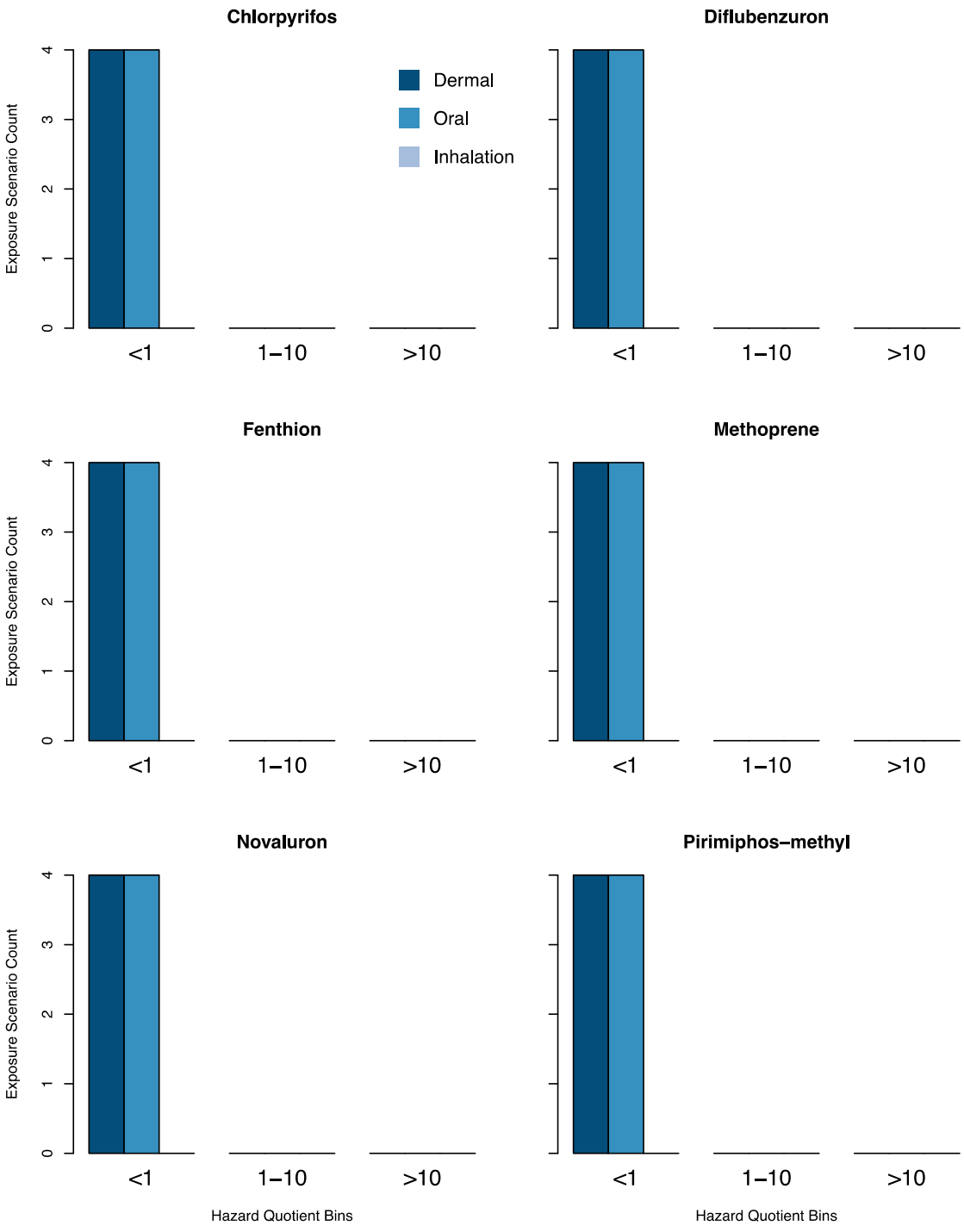

Novaluron
Pirimiphos−methyl
Pyriproxyfen
Temephos (EC)
Temephos (G)
Dermal
Oral
Inhalation
Exposure Scenario Count
0
1
2
<1
1−10
>10
Hazard Quotient Bins

Figure C4-3b. Risk Profiles - Larvicides - All Insecticides - Resident Receptors



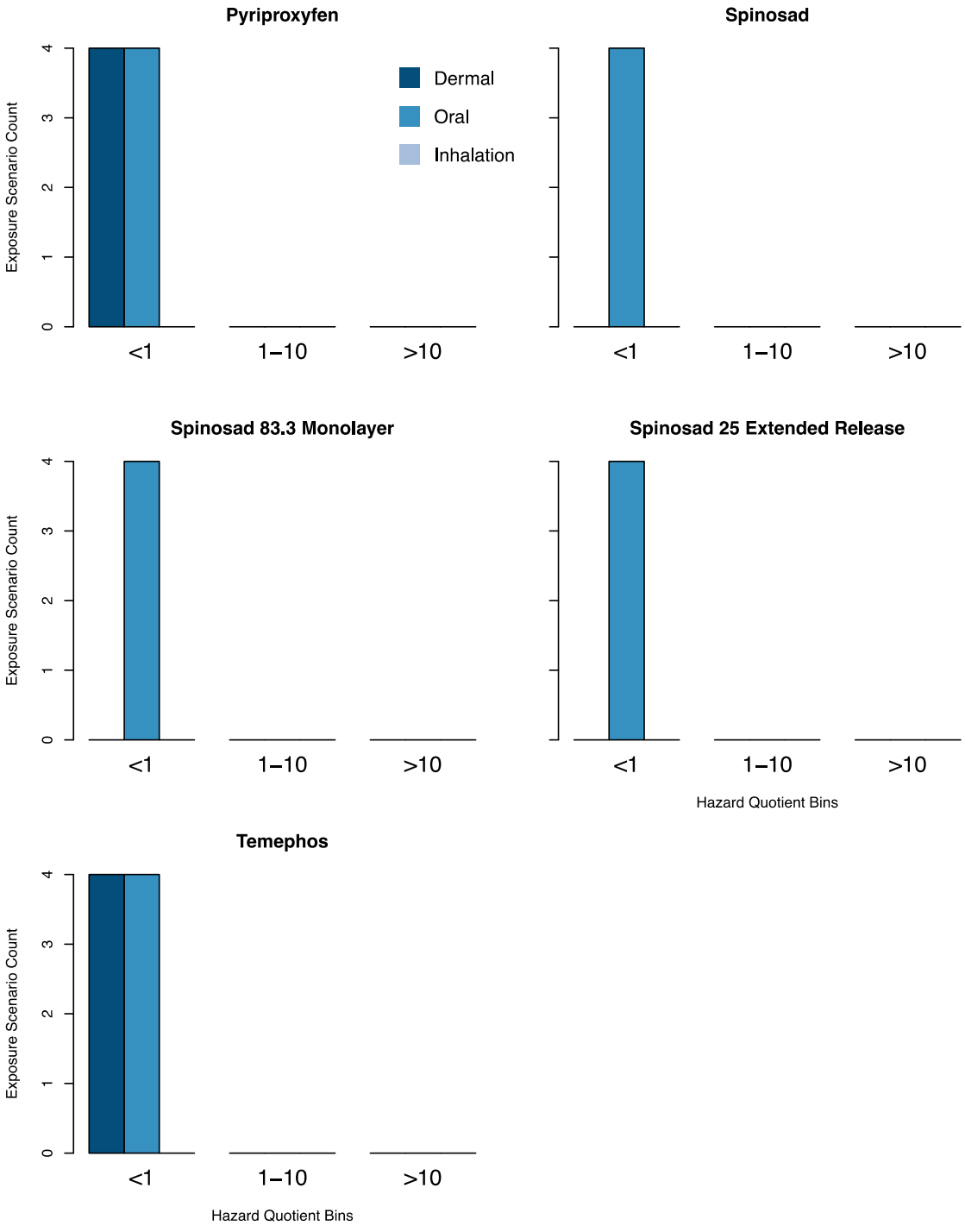
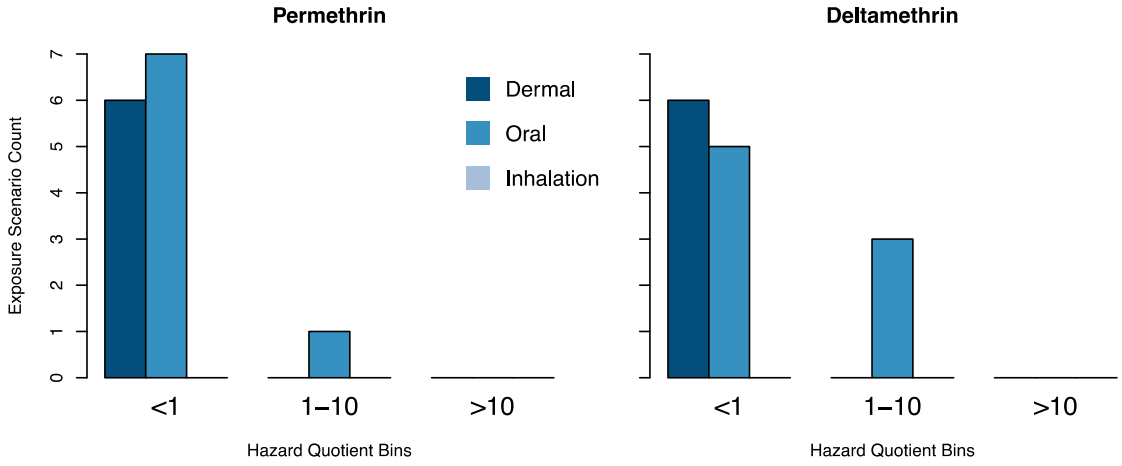

Pyriproxyfen
Spinosad
Spinosad 83.3 Monolayer
Spinosad 25 Extended Release
Temephos
Dermal
Oral
Inhalation
Exposure Scenario Count
0
1
2
3
4
<1
1–10
>10
Hazard Quotient Bins

Figure C4-4. Risk Profiles - Hammocks - All Insecticides - Resident Receptors



ANNEX D-1: INPUT PARAMETER TABLES

Table D-1: Chemical/Physical Properties

Alpha Cypermethrin (67375-30-8)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atm-cu m/mol)			9.50E06	Toxnet	
Melting Point (K)	351.15	354.15	352.65	Toxnet	
Molecular Weight (g/mol)			416.3	Toxnet	
Organic carbon partition coefficient (Koc) ml/g			142,000	Toxnet	
Octanol-water partition coefficient (log Kow)			6.94	Toxnet	
Half-life in air (d)			0.75	Toxnet	Hydroxyl radicals
Half-life in soil (d)	7	14	10.5	Toxnet	
Half-life in water (d) Photolysis			8	Toxnet	Model river
Half-life in water (d) Hydrolysis			65	Toxnet	Model lake
Solubility (mg/L)	0.005	0.01	0.01	Toxnet	
Vapor pressure (Pa)			7.83E-05	Toxnet	

Chlorfenapyr (122453-73-0)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atmcu m/mol)			5.70E-09	Toxnet	
Melting Point (K)	373.15	374.15	373.65	Toxnet	
Molecular Weight (g/mol)			407. 62	Toxnet	
Octanolwater partition coefficient (log Kow)			4.83	Toxnet	
Organic carbon partition coefficient (Koc) ml/g	10, 000	11, 500	11,750	Toxnet	
Halflife in air (d)			1.2	Toxnet	
Halflife in soil (d)	230	250	240	Toxnet	Aerobic

Chlorfenapyr (122453-73-0)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Halflife in soil (d)			250	Toxnet	Anaerobic
Halflife in water (d) Photolysis	5	7	6	Toxnet	
Halflife in water (d) Hydrolysis			> 30	Toxnet	
Solubility (mg/L)			0. 14	Toxnet	pH 7
Vapor pressure (Pa)			5.40E-06	Toxnet	

Chlorpyrifos (2921-88-2)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atmcu m/mol)			3.55E-05	Toxnet	at 25 deg C
Melting Point (K)	314.15	315.15	314.65	Toxnet	
Molecular Weight (g/mol)			350.59	Toxnet	
Octanol water partition coefficient (log Kow)			5	Toxnet	
Organic carbon partition coefficient (Koc) ml/g	995	31000	15998	Toxnet	
Halflife in air (d)			0.2	Toxnet	
Halflife in soil (d)	4	139	42	Toxnet	7-15 d for surface, 33-56 d for soil incorporation
Halflife in water (d) Photolysis	4.2	9.7	7	Toxnet	min-summer, max-winter
Halflife in water (d) Hydrolysis	16	72	72	Toxnet	at 25 deg C, pH 7, min value is for pH 9
Solubility (mg/L)	1.12	1.4	1.4	Toxnet	at 25 deg C
Vapor pressure (Pa)			2.69E-03	Toxnet	at 25 deg C

Clothianidin (210880-92-5)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atm-cu m/mol)			2.90E-16	Toxnet	at 20 deg C
Melting Point (K)			450	Toxnet	
Molecular Weight (g/mol)			249.7	Toxnet	
Organic carbon partition coefficient (Koc) ml/g			60	Toxnet	
Octanol-water partition coefficient (log Kow)			0.7	Toxnet	at 25 deg C
Half-life in air (d)			n/a	Toxnet	Exists solely in the particulate phase in the ambient atmosphere.
Half-life in soil (d)			34	Toxnet	
Aquatic half-life (d)			27	Toxnet	
Half-life in water (d) Photolysis			>1	Toxnet	
Half-life in water (d) Hydrolysis			n/a	Toxnet	Hydrolysis not expected to occur, lack of hydrolyzable functional groups
Solubility (mg/L)			327	Toxnet	at 20 deg C
Vapor pressure (Pa)			1.31E-07	Toxnet	

Deltamethrin (52918-63-5)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atmcu m/mol)			5. 00E06	Toxnet	
Melting Point (K)			370	Toxnet	
Molecular Weight (g/mol)			505.2	Toxnet	
Octanolwater partition coefficient (log Kow)			5.43	NIOSH	
Organic carbon partition coefficient (Koc) ml/g	79000	16300000	8,189,500	Toxnet	

Deltamethrin (52918-63-5)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Halflife in air (d)			NF		
Halflife in soil (d)	34.3	48.3	41.3	Toxnet	
Halflife in water (d) Photolysis	1	5	3	Toxnet	
Halflife in water (d) Hydrolysis			stable	Toxnet	
Solubility (mg/L)			2. 00E03	Toxnet	At 20 deg C, reported as < value
Vapor pressure (Pa)			1.20E-07	Toxnet	

Diflubenzuron (35367-38-5)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atmcu m/mol)			4.60E-09	Toxnet	
Melting Point (K)			501.15	Toxnet	
Molecular Weight (g/mol)			310.68	Toxnet	
Octanolwater partition coefficient (log Kow)			3.89	Toxnet	
Organic carbon partition coefficient (Koc) ml/g	6790	10600	8695	Toxnet	
Halflife in air (d)			n/a	Toxnet	Exists solely in the particulate phase in the ambient atmosphere.
Halflife in soil (d)	2	35	14	Toxnet	
Halflife in water (d) Photolysis			80	Toxnet	
Halflife in water (d) Hydrolysis	32.5	180	180	Toxnet	at 25 deg C, pH 7, minimum value at pH 9
Solubility (mg/L)			0.08	Toxnet	at 25 deg C, pH 7
Vapor pressure (Pa)			1.20E-07	Toxnet	

Fenthion (55-38-9)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atmcu m/mol)			1.46E-06	Toxnet	
Melting Point (K)			280.15	Toxnet	
Molecular Weight (g/mol)			278.34	Toxnet	
Octanolwater partition coefficient (log Kow)			4.09	Toxnet	
Organic carbon partition coefficient (Koc) ml/g	1400	4000	2700	Toxnet	
Halflife in air (d)			0.2	Toxnet	
Halflife in soil (d)			34	Toxnet	
Halflife in water (d) Photolysis	2.9	19.7	11.3	Toxnet	
Halflife in water (d) Hydrolysis			101.7	Toxnet	
Solubility (mg/L)			7.5	Toxnet	at 20 deg C
Vapor pressure (Pa)			4.00E-03	Toxnet	

Methoprene (40596-69-8)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atmcu m/mol)			6. 90E06	Toxnet	
Melting Point (K)			298.15	CMMCP, 2005	
Molecular Weight (g/mol)			310.48	Toxnet	
Octanolwater partition coefficient (log Kow)			5.50	Toxnet	
Organic carbon partition coefficient (Koc) ml/g			23000	Toxnet	
Halflife in air (d)	0.033	0.0623	0.047	Toxnet	
Halflife in soil (d)			10.00	Toxnet	
Halflife in water (d)			13	Toxnet	
Halflife in water (d)			6.3	Toxnet	model river
Halflife in water (d)			75	Toxnet	model lake
Solubility (mg/L)			1.4	Toxnet	Room temperature
Vapor pressure (Pa)			3.02E-02	Toxnet	at 25 deg C

Novaluron (116714-46-6)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atmcu m/mol)			n/a	Health Canada, 2006	
Melting Point (K)	449.15	452.15	450.65	Toxnet	
Molecular Weight (g/mol)			492.7	Toxnet	
Octanolwater partition coefficient (log Kow)			5.27	Toxnet	
Organic carbon partition coefficient (Koc) ml/g	6030	11828	8929	Health Canada, 2006	
Halflife in air (d)			n/a	Health Canada, 2006	non-volatile
Halflife in soil (d)	4	>120	31.3	Health Canada, 2006	
Halflife in water (d) Photolysis			139	FAO, 2004	12 hours daylight, pH 5
Halflife in water (d) Hydrolysis			stable	FAO, 2004	pH 7 at 25 deg C
Halflife in water (d) Hydrolysis			101	FAO, 2004	pH 9 at 25 deg C
Solubility (mg/L)			0.9531	Toxnet	
Vapor pressure (Pa)			5.00E-04	Toxnet	

Permethrin (52645-53-1)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atmcu m/mol)			2.40E-06	Toxnet	
Melting Point (K)			293.15	Toxnet	

Permethrin (52645-53-1)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Molecular Weight (g/mol)			391.29	Toxnet	
Octanolwater partition coefficient (log Kow)			6.5	Toxnet	
Organic carbon partition coefficient (Koc) ml/g	10471	86000	48,235	Toxnet	
Halflife in air (d)			0.71	Toxnet	Hydroxyl radical
Halflife in air (d)			49.00	Toxnet	Ozone
Halflife in soil (d)	4	40	30.00	Toxnet	Aerobic
Halflife in soil (d)	3	204	108.00	Toxnet	Anaerobic
Halflife in water (d) Photolysis	23	37	30	Toxnet	
Halflife in water (d) Hydrolysis			stable	Toxnet	
Solubility (mg/L)			0.0111	Toxnet	
Vapor pressure (Pa)			6.90E-06	Toxnet	At 25 deg C

Piperonyl butoxide (51-03-6)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atmcu m/mol)			8.9E11	Toxnet	
Melting Point (K)			<293.15	SCBT, 2016	Liquid at room temp
Molecular Weight (g/mol)			338. 43	Toxnet	
Octanolwater partition coefficient (log Kow)			4.75	Toxnet	
Organic carbon partition coefficient (Koc) ml/g	399	830	584	Toxnet	
Halflife in air (d)			0.15	Toxnet	
Half-life in soil (d)			14	Toxnet	Aerobic
Halflife in water (d) Photolysis			0.35	Toxnet	
Halflife in water (d) Hydrolysis			stable	Toxnet	
Solubility (mg/L)			14.3	Toxnet	At 25 deg C
Vapor pressure (Pa)			2.11E-05	Toxnet	At 25 deg C

Pirimiphos-Methyl (29232-93-7)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atmcu m/mol)			6.07E-07	Toxnet	
Melting Point (K)	288.15	291.15	289.65	Cornell, 1985	
Molecular Weight (g/mol)			305.33	Toxnet	
Octanolwater partition coefficient (log Kow)			4.12	Toxnet	
Organic carbon partition coefficient (Koc) ml/g	950	8500	4725	Toxnet	
Halflife in air (d)			0.1	Toxnet	
Halflife in soil (d)	5.2	5.9	5.6	Toxnet	
Halflife in water (d) Photolysis			NF	Toxnet	Varies too much depending on condition
Halflife in water (d) Hydrolysis	7.3	79	79	Toxnet	pH 7, min at pH 5
Solubility (mg/L)	9.7	11	10	Toxnet	At 20 deg C, pH 7; min-pH 9; max-pH 5
Vapor pressure (Pa)			2.00E-03	Toxnet	At 20 deg C

Pyriproxyfen (95737-68-1)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atmcu m/mol)			6.30E-10	Toxnet	
Melting Point (K)	318.15	320.15	319.15	Toxnet	
Molecular Weight (g/mol)			321.37	Toxnet	
Octanolwater partition coefficient (log Kow)			5.37	Toxnet	
Organic carbon partition coefficient (Koc) ml/g			405000	Toxnet	
Half-life in air (d)			0.31	Toxnet	
Half-life in soil (d)			12.4	Sullivan	Aerobic
Halflife in water (d)			7.5	Toxnet	

Pyriproxyfen (95737-68-1)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Halflife in water (d) photolysis	3.72	6.23	4.98	Sullivan	
Halflife in water (d) hydrolysis			Stable	Sullivan	
Solubility (mg/L)			0.367	Sullivan	
Vapor pressure (Pa)			1.33E-05	Toxnet	

Spinosad = Spinosyn A (131929-60-7) (85% concentration)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atmcu m/mol)			9.82E10	Kollman	
Melting Point (K)	357.15	372.65	364.9	Toxnet	
Molecular Weight (g/mol)			731.95	Toxnet	
Octanolwater partition coefficient (log Kow)			2.8	Toxnet	
Organic carbon partition coefficient (Koc) ml/g			35838	Kollman	
Reaction half-life in air (d)			<1	Kollman	Not volatile
Photolysis half-life in soil (d)			8.68	Kollman	
Half-life in soil (d)			17.3	Kollman	Aerobic
Half-life in soil (d)			161	Kollman	Anaerobic
Halflife in water (d) hydrolysis			>30	Kollman	25 deg C, pH 7
Halflife in water (d) hydrolysis			200	Kollman	25 deg C, pH 9
Half-life in water (d) photolysis			0.96	Kollman	
Solubility (mg/L)			89.4	Toxnet	
Vapor pressure (Pa)			4.00E-09	Toxnet	

Spinosad = Spinosyn D (131929-63-0) (15%)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atmcu m/mol)			4.87E7	Kollman	
Melting Point (K)	434.15	443.15	438.9	Kollman	
Molecular Weight (g/mol)			745.99	Dow, 2001	Dow Technical Bulletin
Octanolwater partition coefficient (log Kow)			4.53	Dow, 2001	pH 7
Organic carbon partition coefficient (Koc) ml/g			32000	Thompson	
Reaction halflife in air (d)			<1	Kollman	Not volatile
Photolysis half-life in soil (d)			9.44	Kollman	
Half-life in soil (d)			14.5	Kollman	Aerobic
Half-life in soil (d)			250	Kollman	Anaerobic
Half-life in water (d) photolysis			0.84	Kollman	
Halflife in water (d) hydrolysis			>30	Kollman	25 deg C, pH 7
Halflife in water (d) hydrolysis			259	Kollman	25 deg C, pH 9
Solubility (mg/L)			0.495	Toxnet	
Vapor pressure (Pa)			2.13E-08	Kollman	

Temephos (3383-96-8)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Henry's law constant (atmcu m/mol)			2.00E-09	Toxnet	At 25 deg C
Melting Point (K)	303.15	303.65	303.4	Toxnet	
Molecular Weight (g/mol)			466.48	Toxnet	
Octanolwater partition coefficient (log Kow)			5.96	Toxnet	
Organic carbon partition coefficient (Koc) ml/g	18250	31800	25,025	Toxnet	
Halflife in air (d)			0.117	Toxnet	
Halflife in soil (d)			30.00	EXTOXNET, 2005	

Temephos (3383-96-8)

Parameter	Minimum Value	Maximum Value	Mean Value	Reference	Comment
Half life in water (d) biodegredation			17.20	Toxnet	
Halflife in water (d) photolysis			400	Toxnet	River water
Halflife in water (d) hydrolysis			106	Toxnet	pH 7
Solubility (mg/L)			0.001	EXTOXNET, 2005	At 20 deg C
Vapor pressure (Pa)			1.05E-05	Toxnet	At 25 deg C

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TABLE D-2: PESTICIDE USE DATA

INDOOR RESIDUAL SPRAYS

Vector management practice	Pesticide formulation	Parameter	Minimum Value	Maximum Value	Mean Value	Comments	Reference
Chlorfenapyr	240 SC	Application (kg ai/m2)			2.50E-04	Phantom	WHOPES, 2013
Chlorfenapyr	240 SC	Application frequency (times/year)	0	5.8	5.8	Duration of effective action 0 to 9 weeks	WHOPES, 2013
Clothianidin	WG	Application (kg ai/m2)			3.00E-04	Sumishield	Sumitomo Chemical, 2014
Clothianidin	WG	Application frequency (times/year)			1.7	Duration of effective action 7 months	Sumitomo Chemical, 2014
Clothianidin	WP-SB	Application (kg ai/m2)			2.00E-04	Fludora Fusion	Bayer, 2016
Deltamethrin	WP-SB	Application (kg ai/m2)			2.50E-05	Fludora Fusion	Bayer, 2016
Clothianidin, Deltamethrin	WP-SB	Application frequency (times/year)			2	Fludora Fusion	Bayer, 2016
Deltamethrin	WP	Application (kg ai/m2)	2.00E-05	2.50E-05	2.25E-05		WHO, 2015
Deltamethrin	WP, WDG	Application frequency (times/year)	2	4	3	Duration of effective action 3-6 months	WHO, 2015
Pirimiphos-methyl	WP, EC	Application (kg ai/m2)	1. 00E-03	2. 00E-03	1.50E-03		WHO, 2015

Vector management practice	Pesticide formulation	Parameter	Minimum Value	Maximum Value	Mean Value	Comments	Reference
Pirimiphos-methyl	WP, EC	Application frequency (times/year	4	6	5		WHO, 2015
Pirimiphos-methyl	CS	Application (kg ai/m2)			1.00E-03	Actellic 300 CS	WHO, 2015
Pirimiphos-methyl	CS	Application frequency (times/year	2	3	2.5	Actellic 300 CS	WHO, 2015

LARVICIDES

Vector management practice	Pesticide formulation	Parameter	Minimum Value	Maximum Value	Mean Value	Comments	Reference
Chlorpyrifos	EC	Application (kg ai/m2)	1.10E-06	2.50E-06	1.80E-06		WHOPES, 2016
Diflubenzuron	DT, G, WP	Application (kg ai/m2)	2.50E-06	1.00E-05	6.25E-06		WHOPES, 2016
Fenthion	EC	Application (kg ai/m2)	2.20E-06	1.12E-05	6.70E-06		WHOPES, 2016
Methoprene	EC	Application (kg ai/m2)	2.00E06	4.00E06	3.00E-06		Najera and Ziam, 2002
Novaluron	EC	Application (kg ai/m2)	2.50E-06	1.00E-05	6.25E-06		WHOPES, 2016
Pirimiphos-methyl	EC	Application (kg ai/m2)	5.00E-06	5.00E-05	2.75E-05		WHOPES, 2016

Vector management practice	Pesticide formulation	Parameter	Minimum Value	Maximum Value	Mean Value	Comments	Reference
Pyriproxyfen	Sumilarv 0.5 G	Application (kg ai/m2)	1.00E-06	5.00E-06	3.00E-06		WHOPES, 2016
Spinosad	DT, EC, G, SC	Application (kg ai/m2)	2.00E-06	5.00E-05	2.60E-05		WHOPES, 2016
Spinosad	83.3 monolayer DT	Application (kg ai/m2)	2.50E-05	5.00E-05	3.75E-05		WHOPES, 2016
Spinosad	25 extended release G	Application (kg ai/m2)	2.50E-05	4.00E-05	3.25E-05	Open bodies of water	WHOPES, 2016
Spinosad	25 extended release G	Application (kg ai/m2)	1.00E-04	1.50E-04	1.25E-04	Control of *Culex quinquefsciatus* in open bodies of water with high organic matter	WHOPES, 2016
Temephos	EC, G	Application (kg ai/m2)	5. 60E06	1. 12E05	8.40E-06		WHOPES, 2016
Bacillus thuringiensis israelensis, strain AM65-52 (3000 ITU/mg)	WG	Application (kg ai/m2)	1.25E-05	7.50E-05	4.69E-05		WHOPES, 2016
Bacillus thuringiensis israelensis, strain AM65-52 (200 ITU/mg)	GR	Application (kg ai/m2)	5.00E-04	2.00E-03	1.25E-03		WHOPES, 2016
Bacillus thuringiensis israelensis, strain AM65-52 + *B. sphaericus* strain ABTS-1743; 50 Bsph ITU/mg)	GR	Application (kg ai/m2)	5.00E-04	2.00E-03	1.25E-03		WHOPES, 2016

Vector management practice	Pesticide formulation	Parameter	Minimum Value	Maximum Value	Mean Value	Comments	Reference
Bacillus thuringiensis israelensis, strain 266/2 (>=1200 ITU/mg)	SC	Application (mL ai/m2)	3.00E+00	5.00E+00	4.00E+00		WHOPES, 2016

LONG-LASTING INSECTICIDE NETS

Active Ingredient	Active Ingredient (mg ai/m2)	Comments	Reference
Alpha-cypermethrin	100	Interceptor G2	BASF, 2014
Chlorfenapyr	200	Interceptor G2	BASF, 2014
Permethrin	800	Olyset Duo	Bowen, 2011
Pyriproxyfen	400	Olyset Duo	Bowen, 2011
Permethrin	800	Olyset Plus	Sumitomo, 2016
Piperonyl butoxide	400	Olyset Plus	Sumitomo, 2016
Deltamethrin	76	Panda Net 2.0	Life Ideas Textiles, 2016

Active Ingredient	Active Ingredient (mg ai/m2)	Comments	Reference
Alpha-cypermethrin	225	Royal Guard	Personal communication, Disease Control Technologies, 2016
Pyriproxyfen	225	Royal Guard	Personal communication, Disease Control Technologies, 2016
Alpha-cypermethrin	261	Royal Sentry	Disease Control Technologies, 2016

CLOTHING AND HAMMOCKS

Vector management practice	Active Ingredient (mg ai/kg)	Comments	Reference
Permethrin	1250	Clothing	WHOPES, 2000
Permethrin	1500	Hammock	WHO, 1997

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ANNEX D-3. HUMAN HEALTH BENCHMARKS USED IN THE RISK ASSESSMENT

Alpha-cypermethrin (52315-07-8) – synthetic pyrethroid

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
Acute	Oral	0.1	Incidental oral NOAEL of 10 mg/kg/day for acute neurotoxicity study in rat with zeta-cypermethrin based on clinical signs of neurotoxicity and changes in FOB. LOC for MOE = 100 per USEPA	USEPA, 2008
Intermediate	Oral	0.05	Incidental oral NOAEL of 5 mg/kg/day from neurotoxicity study in the rat with zeta-cypermethrin; neurological effects included decreased motor activity, food consumption. LOC for MOE = 100 per USEPA	USEPA, 2008
Chronic	Oral	0.006	Chronic oral NOAEL of 0.6 mg/kg/day from feeding study in the dog, based on clinical signs of neurotoxicity and mortality in males. UF of 100 (10A, 10H) applied by USEPA	USEPA, 2008
Acute	Dermal	5	Single dermal application for rats and mice of 500 mg/kg based on no signs of intoxication or mortality. UF of 100 applied per EPA guidance[1]	IPCS, 1992
Intermediate	Dermal	5	Single dermal application for rats and mice of 500 mg/kg based on no signs of intoxication or mortality. UF of 100 applied per EPA guidance[1]	IPCS, 1992
Chronic	Dermal	0.006	Chronic oral NOAEL of 0.6 mg/kg/day from feeding study in the dog, based on clinical signs of neurotoxicity and mortality in males (dermal absorption factor for long-term exposure = 2.5%). Occupational LOC for MOE = 100 per USEPA	USEPA, 2008
Acute	Inhalation	0.027	Inhalation NOAEL of 2.7 mg/kg/day (0.01 mg/L) from 21-day inhalation study in the rat, based on decrease in body weight and salivation. Occupational and residential LOC for MOE =100 per USEPA	USEPA, 2008
Intermediate	Inhalation	0.027	Inhalation NOAEL of 2.7 mg/kg/day (0.01 mg/L) from 21-day inhalation study in the rat, based on decrease in body weight and salivation. Occupational and residential LOC for MOE =100 per USEPA	USEPA, 2008
Chronic	Inhalation	0.009	Inhalation NOAEL of 2.7 mg/kg/day (0.01 mg/L) from 21-day inhalation study in the rat, based on decrease in body weight and salivation. Occupational LOC for MOE =300 because of the lack of chronic study per USEPA	USEPA, 2008

[1] https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments

Chlorfenapyr (122453-73-0) – pro-insecticide, halogenated pyrrole

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
Acute	Oral	0.45	Oral NOAEL of 45 mg/kg/day from a gastric intubation study, based on neurological tests (FOB) and neuropathologic lesions. UF of 100 (10A, 10H) was applied per USEPA guidance[1]	USEPA, 2001
Intermediate	Oral	0.045	Acute benchmark adopted with a UF of 10 applied to account for difference in exposure duration (10S).	USEPA, 2001
Chronic	Oral	0.026	Oral NOAEL of 2.6 mg/kg/day from one-year dietary study in rats, based on neurotoxic effects (myelinopathic alterations) and other behavior effects. UF of 100 (10A, 10H) applied per USEPA guidance[1]	USEPA, 2001
Acute	Dermal	1	NOAEL of 100 mg/kg/day from 28-day dermal toxicity study in rabbits, based on increased cholesterol and liver effects. UF of 100 applied per USEPA guidance[1]	USEPA, 2001
Intermediate	Dermal	1	NOAEL of 100 mg/kg/day from 28-day dermal toxicity study in rabbits, based on increased cholesterol and liver effects. UF of 100 (10A, 10H) applied per USEPA guidance[1]	USEPA, 2001
Chronic	Dermal	0.026	Oral NOAEL of 2.6 mg/kg/day from one-year dietary study in rats, based on neurotoxic effects (myelinopathic alterations) and other behavior effects. Dermal absorption factor of 5% recommended for long-term exposure. UF of 100 applied per USEPA guidance[1]	USEPA, 2001
Acute	Inhalation	0.042	Oral NOAEL of 4.2 mg/kg/day from subchronic study on dogs, based on reduced body weight gain, feed efficiency, and emaciation. Inhalation absorption factor of 100% is recommended. UF of 10 (10A, 10H) applied per USEPA guidance[1]	USEPA, 2001
Intermediate	Inhalation	0.042	Oral NOAEL of 4.2 mg/kg/day from subchronic study on dogs, based on reduced body weight gain, feed efficiency, and emaciation. Inhalation absorption factor of 100% is recommended. UF of 100 (10A, 10H) applied per USEPA guidance[1]	USEPA, 2001
Chronic	Inhalation	0.026	Oral NOAEL of 2.6 mg/kg/day from chronic study on rats, based on body weight gains, brain lesions, and scabbing of skin. Inhalation absorption factor of 100% is recommended. UF of 100 (10A, 10H) applied per USEPA guidance[1]	USEPA, 2001

[1] https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments

Chlorpyrifos (2921-88-2) – organophosphate

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
Acute	Oral (food)	0.0047	Oral acute point of departure (PoD) of 467 µg/kg/day from PBPK-PD model for adult female subgroup (Table 4.8.4). Acute PAD calculated by USEPA applying a UF of 100 (10x intraspecies, 10x FQPA safety factor).	USEPA, 2014
Intermediate Chronic	Oral (food)	0.00078	21-day exposure PoD of 78 µg/kg/day from PBPK-PD model for adult female subgroup (Table 4.8.4). Intermediate PAD calculated by USEPA applying a UF of 100 (10x intraspecies, 10x FQPA safety factor).	USEPA, 2014
Acute	Oral (water)	0.0042	Based on oxon derivative. Oral acute PoD of 1183 µg/L from PBPK-PD model for infant subgroup (Table 4.8.4). Acute PAD calculated by assuming 0.68856 L/d and 4.8 kg body weight, and applying USEPA's UF of 40 (4x intraspecies, 10x FQPA safety factor).	USEPA, 2014
Intermediate Chronic	Oral (water)	0.00078	Based on oxon derivative. 21-day exposure PoD of 217 µg/kg/day from PBPK-PD model for infant subgroup (Table 4.8.4). Intermediate PAD calculated by assuming 0.68856 L/d and 4.8 kg body weight, and applying USEPA's UF of 40 (4x intraspecies, 10x FQPA safety factor).	USEPA, 2014
Intermediate Chronic	Dermal	0.036	21-day exposure PoD of 3630 µg/kg/day from PBPK-PD model for adult female occupational subgroup (Table 4.8.4). Intermediate PAD calculated by USEPA applying a UF of 100 (10x intraspecies, 10x FQPA safety factor).	USEPA, 2014
Intermediate Chronic	Inhalation	0.0014	21-day exposure PoD of 138 µg/kg/day from PBPK-PD model for adult female occupational subgroup (Table 4.8.4). Intermediate PAD calculated by USEPA applying a UF of 100 (10x intraspecies, 10x FQPA safety factor).	USEPA, 2014

Clothianidin (67375-30-8) – nitroguanidine neonicotinoid

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
Acute Intermediate Chronic	Oral	0.0098	NOAEL of 9.8 mg/kg/day from a two-generation reproduction study on rats, based on decreased body weight gain, delayed sexual maturation, an increase in stillbirths in both generations. UF of 100 (10A, 10H) and an MF of 10 (lack of developmental immunotoxicity study) applied by USEPA	USEPA, 2012
Acute Intermediate Chronic	Dermal	0.0098	USEPA determined that the same study and same derived benchmark should be used for all durations for dermal exposure.	USEPA, 2012

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
Acute Intermediate Chronic	Inhalation	0.0098	USEPA determined that the same study and same derived benchmark should be used for all durations for dermal exposure. 100% absorption and no portal of entry effect was assumed	USEPA, 2012

Deltamethrin (52918-63-5) – synthetic pyrethroid

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
Acute	Oral	0.005	$BMDL_{1SD}$ of 2.48 mg/kg calculated[1] based on study data on neurological effects (decreased motor activity) in rats. Acute RfD calculated by USEPA applying a UF of 100 (10A, 10H) and SF of 3.	USEPA, 2004
Intermediate	Oral	0.005	Same benchmark used based on USEPA's finding that there is no apparent increase in hazard associated with repeated/chronic exposures	USEPA, 2004
Chronic	Oral	0.005	Same benchmark used based on USEPA's finding that there is no apparent increase in hazard associated with repeated/chronic exposures	USEPA, 2004
Acute	Dermal	10	Dermal NOAEL of 1000 mg/kg/day for rats based on local effects on the skin. Author applied a UF of 100 (10A, 10H).	Barlow et al, 2001
Intermediate	Dermal	10	Same benchmark used based on USEPA's finding that there is no apparent increase in hazard associated with repeated/chronic exposures	Barlow et al, 2001
Chronic	Dermal	10	Same benchmark used based on USEPA's finding that there is no apparent increase in hazard associated with repeated/chronic exposures	Barlow et al, 2001
Acute	Inhalation	0.005	$BMDL_{1SD}$ of 2.48 mg/kg calculated[1] based on study data on neurological effects (decreased motor activity) in rats. Acute RfD calculated by USEPA applying a UF of 100 (10A, 10H) and SF of 3. Inhalation absorption assumed to be 100%.	USEPA, 2004
Intermediate	Inhalation	0.005	Same benchmark used based on USEPA's finding that there is no apparent increase in hazard associated with repeated/chronic exposures	USEPA, 2004
Chronic	Inhalation	0.005	Same benchmark used based on USEPA's finding that there is no apparent increase in hazard associated with repeated/chronic exposures	USEPA, 2004

[1]$BMDL_{1SD}$= the 95% lower confidence limit of the central estimate of the dose that results in decreased motor activity compared to control animals based upon one standard deviation using Benchmark Dose Analysis.

Diflubenzuron (35367-38-5) – growth regulator

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
Acute	Oral	–	No endpoint attributable to a single exposure was identified	USEPA, 2014a
Intermediate Chronic	Oral	0.02	NOAEL of 2.0 mg/kg-d based on methemoglobinemia in a 52-week oral study in dogs. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations.)	USEPA, 2014a; USEPA, 1997a
Acute	Dermal	5.0	NOAEL of 500 mg/kg-d based on methemoglobinemia in a 21-day dermal study in rats. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations.)	USEPA, 2014a
Intermediate Chronic	Dermal	0.02	NOAEL of 2 mg/kg-d based on methemoglobinemia in a 13-week oral study in dogs. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations.) A 0.5% absorption factor is suggested for application of the intermediate/chronic benchmark in risk assessment.	USEPA, 2014a
Acute Intermediate	Inhalation	0.2	NOAEL of 20.30 mg/kg-s based on a 28-day inhalation study in rats. No effect observed at highest tested dose. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations.)	USEPA, 2014a
Chronic	Inhalation	0.02	NOAEL of 2.0 mg/kg-d based on methemoglobinemia in a 52-week oral study in dogs. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations.)	USEPA, 2014a; USEPA, 1997a
Chronic	Oral Dermal Inhalation	1.06E-02	Oral study in water and milk. Based on the milk metabolite and water degradate 4-chlorophenylurea (CPU) in National Toxicology Program oral rat study. For dietary exposure from drinking water, the concentration of the CPU degradate was assessed at approximately 70% of the concentration used to assess noncancer effects of diflubenzuron – the published CPU cancer benchmark of 0.0152 per mg/kg-d has been multiplied by 0.7 to reflect this for application to the larvicide drinking water scenario.	USEPA, 2014a

Fenthion (55-38-9) – organophosphate

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
Acute	Oral	0.0007	NOAEL of 0.07 mg/kg-d based on lack of plasma cholinesterase inhibition at week 1 of a 2-year oral monkey study. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations.)	USEPA, 2001b
Intermediate Chronic	Oral	0.00007	LOAEL of 0.02 mg/kg-d based on plasma cholinesterase inhibition in 2-year oral monkey study. A UF of 300 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations, 3x lack of true NOAEL.)	USEPA, 2001b
Acute	Dermal	0.0007	NOAEL of 0.07 mg/kg-d based on lack of plasma cholinesterase inhibition at week 1 of a 2-year oral monkey study. The oral UF of 100 was applied to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations.) A 20% absorption factor based on a single-dose study is protectively applied for application in acute exposure risk assessments.	USEPA, 2001b
Intermediate Chronic	Dermal	0.00007	LOAEL of 0.02 mg/kg-d based on plasma cholinesterase inhibition in 2-year oral monkey study. The oral UF of 300 was applied to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations, 3x lack of true NOAEL.) A 3% absorption factor is suggested by EPA for application in intermediate and chronic exposure risk assessments.	USEPA, 2001b
Acute	Inhalation	0.0007	NOAEL of 0.07 mg/kg-d based on lack of plasma cholinesterase inhibition at week 1 of a 2-year oral monkey study. The oral UF of 100 was applied to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations.)	USEPA, 2001b
Intermediate Chronic	Inhalation	0.00007	LOAEL of 0.02 mg/kg-d based on plasma cholinesterase inhibition in 2-year oral monkey study. The oral UF of 300 was applied to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations, 3x lack of true NOAEL.)	USEPA, 2001b

Methoprene (40596-69-9) **– growth regulator (hormonal)**

Duration	Route	Benchmark (mg/kg-day)	Endpoint	Reference
Acute Intermediate Chronic	Oral	0.4	NOAEL of 37.5 mg/kg/day based on liver pigmentation in mice exposed over 18 months. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations.)	USEPA, 2001
Acute Intermediate Chronic	Dermal	1.0	NOAEL of 100 mg/kg/day based on erythema in rabbits exposed over 30 days. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations.)	ATSDR, 2005
Acute Intermediate Chronic	Inhalation	25	NOAEL of 21,000 mg/kg/day based on rats exposed for 4 hr/day and 5 day/week over 3 weeks. This was adjusted to 2500 mg/kg-d to account for intermittent exposure. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations.)	ATSDR, 2005

Novaluron (116714-46-6) – growth regulator

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
Acute Intermediate	Oral	0.044	NOAEL of 4.38 mg/kg-d based on hematological effects in a 90-day feeding study in rats. MOE of <100; applied as a UF of 100.	USEPA, 2010
Intermediate Chronic	Oral	0.011	NOAEL of 1.1 mg/kg-d based on erythrocyte damage and anemia in chronic feeding study in rats. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations.)	USEPA, 2010; USEPA 2011
Acute	Dermal	–	No toxicity was observed at the highest dose in the dermal study.	USEPA, 2011
Intermediate	Dermal	0.0044	NOAEL of 4.38 mg/kg-d based on hematological effects in a 90-day feeding study in rats. MOE of <100; applied as a UF of 100. A 10% absorption factor is suggested for application in intermediate and chronic risk assessments in EPA 2010.	USEPA, 2010; USEPA 2011
Chronic	Dermal	0.011	NOAEL of 1.1 mg/kg-d based on erythrocyte damage and anemia in chronic feeding study in rats. MOE of <100; applied as a UF of 100. A 10% absorption factor is suggested for application in intermediate and chronic risk assessments in EPA 2010.	USEPA, 2010; USEPA 2011
Acute	Inhalation	0.044	NOAEL of 4.38 mg/kg-d based on hematological effects in a 90-day feeding study in rats. MOE of <100; applied as a UF of 100.	USEPA, 2010; USEPA 2011
Intermediate Chronic	Inhalation	0.011	NOAEL of 1.1 mg/kg-d based on erythrocyte damage and anemia in chronic feeding study in	USEPA 2011

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
			rats. MOE of <100; applied as a UF of 100.	

Permethrin (52645-53-1) – synthetic pyrethroid

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
Acute	Oral	0.25	NOAEL of 25 mg/kg/day from acute neurotoxicity study in rats, based on clinical signs (e.g., abnormal movement) and increased body temperature. UF of 100 (10A, 10H) applied by USEPA.	USEPA, 2005
Intermediate	Oral	0.25	USEPA recommendation to use acute RfD without adjustment	USEPA, 2005
Chronic	Oral	0.25	USEPA recommendation to use acute RfD without adjustment	USEPA, 2005
Acute	Dermal	5	NOAEL of 500 mg/kg/day from 21 day dermal toxicity study in rats based on no effects (no LOAEL was established). UF of 100 (10A, 10H) applied by USEPA.	USEPA, 2005
Intermediate	Dermal	5	USEPA recommendation to use acute RfD without adjustment	USEPA, 2005
Chronic	Dermal	5	USEPA recommendation to use acute RfD without adjustment	USEPA, 2005
Acute	Inhalation	0.11	NOAEL of 11 mg/kg/day from 15 day inhalation study in rats, based on body tremors and hypersensitivity to noise. UF of 100 (10A, 10H) applied by USEPA.	USEPA, 2005
Intermediate	Inhalation	0.11	NOAEL of 11 mg/kg/day from 15 day inhalation study in rats, based on body tremors and hypersensitivity to noise. UF of 100 (10A, 10H) applied by USEPA.	USEPA, 2005
Chronic	Inhalation	0.11	NOAEL of 11 mg/kg/day from 15 day inhalation study in rats, based on body tremors and hypersensitivity to noise. UF of 100 (10A, 10H) applied by USEPA.	USEPA, 2005
Chronic	Oral	9.6E-03	Cancer slope factor based on lung tumors in female mice exposed via the diet	USEPA, 2005
Chronic	Dermal	9.6E-03	Cancer slope factor based on lung tumors in female mice exposed via the diet	USEPA, 2005
Chronic	Inhalation	9.6E-03	Cancer slope factor based on lung tumors in female mice exposed via the diet	USEPA, 2005

Piperonyl butoxide (51-03-6) – synergist EPA

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
Acute	Oral	0.89	NOAEL of 89 mg/kg/day from two-generation reproduction study in rats based on decrease in body weight gain of F1 and F2 pups at postnatal day 21. UF of 100 (10A, 10H) applied	USEPA, 2006

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
			by USEPA	
Intermediate	Oral	0.89	USEPA recommends same reproduction study NOAEL for intermediate duration exposures.	USEPA, 2006
Chronic	Oral	0.16	NOAEL of 15.5 mg/kg/day from chronic oral toxicity study on dogs (dietary), based on body weight gain, liver effects (hepatocellular hypertrophy). UF of 100 (10A, 10H) applied by USEPA	USEPA, 2006
Acute Intermediate Chronic	Dermal	-	USEPA indicated that there were no systemic, developmental, or neurotoxicity concerns at the limit dose, so no quantification required. PBO classified as mild irritant.	USEPA, 2006
Acute	Inhalation	6.3	NOAEL of 630 mg/kg/day for developmental toxicity study in rats based on decrease in maternal weight gain. UF of 100 (10A, 10H) applied by USEPA	USEPA, 2006
Intermediate	Inhalation	0.013	LOAEL of 3.91 mg/kg/day (0.015 mg/L) from subchronic inhalation toxicity study in rats, based on laryngeal hyperplasia and metaplasia. UF of 100 (10A, 10H) and UF of 3 (10L) applied by USEPA	USEPA, 2006
Chronic	Inhalation	0.0039	LOAEL of 3.91 mg/kg/day (0.015 mg/L) from subchronic inhalation toxicity study in rats, based on laryngeal hyperplasia and metaplasia. UF of 1,000 (10A, 10H, 10L) applied by USEPA	USEPA, 2006

Pirimiphos-methyl (29232-93-7) – organophosphate

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
Acute	Oral	0.006	Benchmark dose point of departure of 6.07 mg/kg-d. UF of 1000 (10A, 10H, and 10 for uncertainty in dose-response for neurodevelopmental effects.)	USEPA, 2016
Intermediate	Oral	0.0007	Adopted chronic benchmark for intermediate exposure.	USEPA, 2016
Chronic	Oral	0.0007	Benchmark dose point of departure of 0.73 mg/kg-d for steady-state exposure; all populations up to age 50 yr. UF of 1000 (10A, 10H, and 10 for uncertainty in dose-response for neurodevelopmental effects.)	USEPA, 2016
Acute	Dermal	0.006	Adopted oral benchmark; route extrapolation.	USEPA, 2016
Intermediate	Dermal	0.0007	Adopted chronic benchmark for intermediate exposure. 0.0007 mg/kg-d is also referenced to USEPA (2006): Oral LOAEL of 0.2 mg/kg/day for neurological effects in rats with UF of 300 (10A, 10H, 3L) applied by USEPA for occupational exposures.	USEPA, 2016; USEPA, 2006
Chronic	Dermal	0.0007	Adopted oral benchmark; route extrapolation. Identical to intermediate exposure dermal RfD	USEPA, 2016; USEPA, 2006

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
			from EPA (2006).	
Acute	Inhalation	0.006	Adopted oral benchmark; route extrapolation.	USEPA, 2016
Intermediate	Inhalation	0.0007	Adopted chronic benchmark for intermediate exposure. 0.0007 mg/kg-d is also referenced to USEPA (2006): Oral LOAEL of 0.2 mg/kg/day for neurological effects in rats with UF of 300 (10A, 10H, 3L) applied by USEPA for occupational exposures.	USEPA, 2016; USEPA, 2006
Chronic	Inhalation	0.0007	Adopted oral benchmark; route extrapolation. Identical to intermediate exposure inhalation RfD from EPA (2006).	USEPA, 2016; USEPA, 2006

Pyriproxifen (122453-73-0) – pyridine-based pesticide

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
Acute	Oral	1	NOAEL of 100 mg/kg/day from rat developmental study based on decreased body weight, body weight gain, food consumption. UF of 100 (10A, 10H) applied by USEPA	USEPA, 2016a
Intermediate	Oral	0.35	NOAEL of 35.1 mg/kg/day from subchronic rat study based on body weight changes, anemia, liver effects. UF of 100 (10A, 10H) applied by USEPA	USEPA, 2016a
Chronic	Oral	0.35	NOAEL of 35.1 mg/kg/day from subchronic rat study based on body weight changes, anemia, liver effects. UF of 100 (10A, 10H) applied by USEPA	USEPA, 2016a
Acute	Dermal	-	Based on systemic toxicity NOAEL of 1,000 mg/kg/day (limit dose), quantification of dermal risks are not required for less than chronic exposures.	USEPA, 2016a
Intermediate	Dermal	-	Based on systemic toxicity NOAEL of 1,000 mg/kg/day (limit dose), quantification of dermal risks are not required for less than chronic exposures.	USEPA, 2016a
Chronic	Dermal	0.35	Oral NOAEL of 35.1 mg/kg/day from subchronic rat study based on body weight changes, anemia, liver effects. UF of 100 (10A, 10H) applied by USEPA	USEPA, 2016a
Acute	Inhalation	-	Based on the absence of biologically relevant toxicity at 1.0 mg/L, quantification of inhalation risks for less-than-chronic exposures is not required. No developmental concerns were seen in rats or rabbits.	USEPA, 2016a
Intermediate	Inhalation	-	Based on the absence of biologically relevant toxicity at 1.0 mg/L, quantification of inhalation risks for less-than-chronic exposures is not required. No developmental concerns were seen in rats or rabbits.	USEPA, 2016a
Chronic	Inhalation	0.35	Oral NOAEL of 35.1 mg/kg/day from subchronic rat study based on body weight	USEPA, 2016a

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
			changes, anemia, liver effects. UF of 100 (10A, 10H) applied by USEPA	

Spinosad (A: 131929-60-7, D: 131929-63-0) – bacterial-produced insecticide

Duration	Route	Benchmark (mg/kg-day)	Study and Toxicological Effects	Reference
Acute	Oral	0.049	NOAEL of 4.9 mg/kg/day from subchronic feeding study on dogs, based on microscopic changes in organs, clinical signs of toxicity, and possible liver damage. UF of 100 (10A, 10H) applied by USEPA.	USEPA, 2002
Intermediate	Oral	0.027	NOAEL of 2.7 mg/kg/day from chronic toxicity study on dogs based on effects on parathyroid, lymphatic tissues, and liver function (enzyme levels). UF of 100 (10A, 10H) applied by USEPA.	USEPA, 2002
Chronic	Oral	0.027	NOAEL of 2.7 mg/kg/day from chronic toxicity study on dogs based on effects on parathyroid, lymphatic tissues, and liver function (enzyme levels). UF of 100 (10A, 10H) applied by USEPA.	USEPA, 2002
Acute Intermediate Chronic	Dermal	-	Exposure route ruled out based on (1) lack of concern for pre and/or postnatal toxicity, (2) the molecular structure and size of spinosad, and (3) the lack of dermal or systemic toxicity at the limit dose of 1,000 mg/kg/day in a 21-day dermal toxicity study in rats.	USEPA, 2002
Acute	Inhalation	0.049	Oral NOAEL of 4.9 mg/kg/day from subchronic feeding study on dogs, based on microscopic changes in organs, clinical signs of toxicity, and possible liver damage. UF of 100 (10A, 10H) applied by USEPA. 100% absorption assumed, with no portal of entry effect.	USEPA, 2002
Intermediate	Inhalation	0.049	Oral NOAEL of 4.9 mg/kg/day from subchronic feeding study on dogs, based on microscopic changes in organs, clinical signs of toxicity, and possible liver damage. UF of 100 (10A, 10H) applied by USEPA. 100% absorption assumed, with no portal of entry effect.	USEPA, 2002
Chronic	Inhalation	0.027	Oral NOAEL of 2.7 mg/kg/day from chronic toxicity study on dogs based on effects on parathyroid, lymphatic tissues, and liver function (enzyme levels). UF of 100 (10A, 10H) applied by USEPA. 100% absorption assumed, with no portal of entry effect.	USEPA, 2002

Temephos (3383-96-8) **– organophosphate**

Duration	Route	Benchmark (mg/kg-day)	Endpoint	Reference
Acute Intermediate Chronic	Oral	0.003	NOAEL of 0.3 mg/kg/day for neurological effects based on inhibition of red blood cell cholinesterase in rats exposed over 90 days. A UF of 100 is applied (10x intraspecies, 10x FQPA safety factor per EPA 2001a). Selected by EPA for short-, intermediate-, and long-term assessments.	USEPA, 2001a
Acute Intermediate Chronic	Dermal	0.003	EPA has applied the oral NOAEL and UF to dermal absorption. A 38% absorption factor is suggested for application in acute, intermediate, and chronic risk assessments.	USEPA, 2001a
Acute Intermediate Chronic	Inhalation	0.003	EPA has applied the oral NOAEL and UF to inhalation exposure.	USEPA, 2001a

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Summary information for uncertainty and modifying factors

Definitions taken from,

https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments

Standard Uncertainty Factors (UFs):

- Use a 10-fold factor when extrapolating from valid experimental results in studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population and is

referenced as "10H".

- Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty involved in extrapolating from animal data to humans and is referenced as "10A".
- Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there are no useful long-term human data. This factor is intended to account for the uncertainty involved in extrapolating from less than chronic NOAELs to chronic NOAELs and is referenced as "10S".
- Use an additional 10-fold factor when deriving an RfD from a LOAEL, instead of a NOAEL. This factor is intended to account for the uncertainty involved in extrapolating from LOAELs to NOAELs and is referenced as "10L".

Modifying Factor (MF):

Use professional judgment to determine the MF, which is an additional uncertainty factor that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above; e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

ANNEX D-4. ECOLOGICAL DATA USED IN THE HEAT MAPS

The ecological risk characterization presented in Section 4.3.3 of the PEA provides a summary of representative data related to environmental persistence, bioaccumulation, and ecological toxicity for each larvicide evaluated in the PEA. The summarization is conveyed in a series of "heat maps" where color is used to indicate the relative number of data points within each of three bins that score persistence, bioaccumulation, and ecological toxicity as low, medium, or high. The compilation of persistence, bioaccumulation, and toxicological data that were reviewed to generate the heat maps for the larvicides are primarily from the Toxicology Data Network (Toxnet) databases maintained by the U.S. National Library of Medicine (https://toxnet.nlm.nih.gov).

The Toxnet database was queried using a query string consisting of the larvicide name and a term related to the endpoint of interest. For example, a search related to the environmental persistence, bioaccumulation and ecological toxicity of chlorpyrifos would include the name and one or more terms pertaining to persistence (e.g., half-life, Koc), bioaccumulation (bioconcentration factor, or BCF), and ecotoxicological benchmark data (e.g., LD50, LC50, EC50, NOAEL, and NOEL). The TOXLINE and HSDB databases within Toxnet were the primary resources from where relevant data were compiled.

In most circumstances, all of the relevant data retrieved from the Toxnet queries on each chemical was compiled. However, if there were numerous references, the search was stopped once four values that would represent the different heat map bins (low, medium or high) or four values for each of the ecotoxicity receptor groups (aquatic invertebrate, aquatic plant, fish, terrestrial invertebrate and terrestrial vertebrate) were identified. Similarly, if there were more than four values for a specific ecological receptor group, then the data compilation only included four data points and did not include every data point retrieved. For example, if 12 LD50 values for mallard duck were available, then only 4 were included in the database so long as they consistently represented a similar range (e.g., high, medium or low). If the data were displaying different ranges within the same ecological receptor (e.g., 4 low LD50 values, 4 high LD50 values, 4 low LD50 values), then all data were included. This abbreviated search approach was intended to provide a snapshot of the range of values for each receptor group reported in Toxnet.

In the cases where there was a lack of data available in Toxnet, broader searches were performed by using PubMed (www.pubmed.org) and the World Health Organization (www.who.int/en/) search engines. For example, toxicological data from the prior 2012 PEA were used for methoprene and temephos, and published reports such as "Environmental Fate of Pyriproxyfen" by Jonathan Sullivan (2000) and WHO Specifications and Evaluations for Public Health Pesticides: Novaluron (2004) were also consulted for this data compilation.

The criteria used to score persistence, bioaccumulation, and ecological toxicity as low, medium, or high for display in the heat maps is summarized in Tables 1 through 3. The persistence of a pesticide can be measured by how long the pesticide will remain in various environmental compartments. Half-life values of a pesticide in water, soil and sediment can be used to determine if the chemical will be relatively high, moderate or have a low chance of persistence once it is released in to the environment. Similarly, the octanol-water coefficient (K_{ow}) is ratio of the solubility of a chemical in octanol and water, where low K_{ow} values represent that the chemical will be more hydrophilic and present in water. The organic carbon water coefficient (K_{oc}) is a similar measure that will determine if the chemical will preferentially persist in the soil. The data cut off values for high, medium and low half-life and partition coefficients were compiled to determine a relative scale for persistence. These criteria and the associated references are provided in Table 1.

Table 1. Criteria Values for Scoring Persistence

	Half life in water, soil, and sediment (days)	K_{ow} - water	K_{oc} - soil
High	>180	>20000	>32000
Medium	>60 - 180	3000-20000	30-32000
Low	<60	<3000	<30

Reference: USEPA, 2012; Kent, 2012

The bioaccumulation potential of a pesticide is measured by the bioconcentration factor (BCF) and octanol-water partition coefficient (K_{ow}). The BCF is a measure of the relative concentration of a chemical at equilibrium for an organism (such as a fish) and an environmental medium in which the organism exists (such as water). Both of these measures reflect the tendency of a chemical to accumulate in the fatty tissues of an organism. The criteria cut-off values for high, medium and low were compiled to determine a relative scale for bioaccumulation. These criteria and the associated references are provided in Table 2.

Table 2. Criteria Values for Scoring Bioaccumulation

	Bioconcentration factor (BCF) - Fish	Log K_{ow} - terrestrial systems	Low K_{ow} - aquatic systems
High	>5000	>4 - 6	>5 - 6
Medium	>=1000 - 5000	>=2 - 4	4 - 5, >6
Low	<1000	<2; >6	<4

Reference: ECETOC, 2014; USEPA, 2012

The ecological toxicity potential of a pesticide is measured by evaluating the response in a test population to either administration of the pesticide or environmental exposure. The dosing of the test population may occur once or over a span of time. A common measure of acute toxicity is the median lethal dose (LD50), which is the dose of a substance that kills 50% of a test population. The LC50 is analogous, being the median lethal concentration (for example, in water) that kills 50% of a test population. The median effective concentration (EC50) is similar to the LC50, except that the endpoint is not necessarily lethality. The no observed adverse effect level (NOAEL) or concentration (NOEC) refer to the highest dose, or exposure concentration, where there is no biologically or statistically significant increase in observed adverse effects. NOAEL and NOEC values were used to evaluate potential adverse ecological effects related to chronic exposures. Because pesticide applications in the environment may affect terrestrial and aquatic systems it is necessary to determine the potential toxicity to many different types of environments and receptors to evaluate potential ecological toxicity. The high, medium and low cut off values for toxicity for 12 different ecological receptors is compiled in Table 3.

Table 3. Criteria Values for Scoring Toxicity

	Avian: Oral	Avian: Dietary	Mammals: Oral	Mammals: Dermal	Terrestrial animals	Non-target Insects
Duration	Acute	Acute	Acute	Acute	Chronic	Acute
Test	LD50	LD50	LD50	LD50	NOAEL	LD50
Units	mg/kg	ppm	mg/kg	mg/kg	mg/kg bw	ug/bee
High	<50	<500	<50	<200	<=0.5	<2
Medium	500-50	1000-500	500 - 50	2000 - 200	>0.5 - <=5	2 - 11

Low	>501	>1001	>500	>2000	>5 - <=50	>11
Reference :	USEPA, 2012	USEPA, 2012	USEPA, 2012	WHO, 2010	ILO, 2001	USEPA, 2014

	Microorganisms	**Fish**	**Aquatic Organisms**	**Aquatic invertebrates**	**Soil dwelling Invertebrates**	**Soil dwelling Invertebrates**
Duration	Chronic	Chronic	Acute	Chronic	Acute	Chronic
Test	EC50	LC50	LC50	EC50	EC50	NOEC
Units	mg/kg bw	mg/L	mg/L	mg/L	mg/kg soil dw	mg/kg
High	<10	<=1	<1	<=1	<10	<10
Medium	100-10	>1-10	<10 - 1	>1-10	100-10	100-10
Low	>100	>10-100	>10	>10-100	>100	>100
Reference :	Hartmann et al, 2014	ILO, 2001	USEPA, 2012	ILO, 2001	Hartmann et al, 2014	Hartmann et al, 2014

Specific values related to persistence, bioaccumulation, and ecological toxicity for developing the heat maps for each of the larvicides evaluated in the ecological risk assessment are provided in the following tables.

Chlorpyrifos (2921-88-2) - organophosphate

Persistence Variables	**Value**	**Units**	**Rank**	**Reference**
Half-life soil	4	days	Low	Toxnet
Half-life soil	139	days	Medium	Toxnet
Half-life water	4.2	days	Low	Toxnet
Half-life water	9.7	days	Low	Toxnet
Half-life water	16	days	Low	Toxnet
Half-life water	72	days	Medium	Toxnet
Kow	100000	unitless	Low	Toxnet
Koc	995	unitless	Medium	Toxnet
Koc	31000	unitless	Medium	Toxnet

Bioaccumulation Variables	**Value**	**Units**	**Rank**	**Reference**
Log Kow - aquatic	5	unitless	Medium	Toxnet
BCF - Oyster	1400	unitless	Medium	Toxnet
BCF - Aquatic Org.	58	unitless	Low	Toxnet
BCF - Aquatic Org.	2880	unitless	Medium	Toxnet
BCF - Fish	468	unitless	Low	Toxnet
BCF - Fish	100	unitless	Toxnet	Low
BCF - Fish	4667	unitless	Toxnet	Medium
Log Kow - terrestrial	5	unitless	Toxnet	High

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor2	Scale	Rank	Reference
LC50		48 hours	Daphnia water flea	0.24	ug/L	Aquatic Invert.	Aquatic Org.	High	Toxnet
LC50			Amphipod	0.07	ug/L	Aquatic Invert.	Aquatic Org.	High	TOXLINE
LC50		Acute	Mysid Shrimp	0.04	ug/L	Aquatic Invert.	Aquatic Org.	High	TOXLINE
LC50		Chronic	Grass Shrimp	0.29	ug/L	Aquatic Invert.	Aquatic Org.	High	TOXLINE
LC50		Acute	Grass Shrimp	1.06	ug/L	Aquatic Invert.	Aquatic Org.	High	TOXLINE
LC50			Mysid Shrimp	0.068	ug/L	Aquatic Invert.	Aquatic Org.	High	TOXLINE
LC50		24 hours	Daphnia magna	3.7	ug/L	Aquatic Invert.	Aquatic Org.	High	Toxnet
LC50		48 hours	Daphnia magna	1	ug/L	Aquatic Invert.	Aquatic Org.	High	Toxnet
LC50		Chronic	Fish	<0.01	mg/L	Fish	Fish	High	TOXLINE
LC50		Chronic	Carassius carassius	0.014	mg/L	Fish	Fish	High	TOXLINE
LC50		Chronic	Common Carp	0.149	mg/L	Fish	Fish	High	TOXLINE
LC50		Chronic	Rainbow Trout	0.009	mg/L	Fish	Fish	High	TOXLINE
LC50		Chronic	Labeo Rrohito	0.442	mg/L	Fish	Fish	High	TOXLINE
LC50		Chronic	Goldfish	0.153	mg/L	Fish	Fish	High	TOXLINE
LC50		Chronic	Catfish	2.2	mg/L	Fish	Fish	Medium	TOXLINE
LC50		24 hours	Common carp	1.8	ug/L	Fish	Fish	High	Toxnet
LC50		24 hours	Common carp	3.6	ug/L	Fish	Fish	High	Toxnet
LC50		48 hours	Common carp	1.4	ug/L	Fish	Fish	High	Toxnet
LC50		48 hours	Common carp	2.8	ug/L	Fish	Fish	High	Toxnet
EC50		48 hours	Bluegill	1.78	ug/L	Fish	Fish	High	Toxnet
LC50		96 hours	Bluegill	10	ug/L	Fish	Fish	High	Toxnet

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor2	Scale	Rank	Reference
LC50		96 hours	Bluegill	5.8	ug/L	Fish	Fish	High	Toxnet
LC50		96 hours	Bluegill	30	ug/L	Fish	Fish	High	Toxnet
EC50		48 hours	Fathead minnow	131.2	ug/L	Fish	Fish	High	Toxnet
EC50		48 hours	Fathead minnow	133.9	ug/L	Fish	Fish	High	Toxnet
LC50		24 hours	Fathead minnow	320	ug/L	Fish	Fish	High	Toxnet
LC50		48 hours	Fathead minnow	248	ug/L	Fish	Fish	High	Toxnet
LD50		Acute	Honeybee	1.14	ug/bee	Terr Invert	Non-target Insects	High	Toxnet
LC50		Acute	Earthworm	390	mg/kg	Terr. Invert.	Soil dwelling Invertebrates	Medium	TOXLINE
LC50		Acute	Earthworm	330	mg/kg	Terr. Invert.	Soil dwelling Invertebrates	Medium	TOXLINE
LC50		Acute	Earthworm	180	mg/kg	Terr. Invert.	Soil dwelling Invertebrates	Medium	TOXLINE
LD50	Oral		Domestic goat	500-1000	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral	Acute	Guinea pig	504	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral	Acute	Mice	152	mg/kg	Terr. Vert.	Mammals: Oral	Medium	TOXLINE
LD50	Oral		Mouse	102	mg/kg	Terr. Vert.	Mammals: Oral	Medium	Toxnet
LD50	Oral		Mouse	152	mg/kg	Terr. Vert.	Mammals: Oral	Medium	Toxnet
LD50	Oral		Mouse	60	mg/kg	Terr. Vert.	Mammals: Oral	Medium	Toxnet
LD50	Oral		Rabbit	1000	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor2	Scale	Rank	Reference
LD50	Oral		Rat	151	mg/kg	Terr. Vert.	Mammals: Oral	Medium	Toxnet
NOAEL	Oral	Chronic	Rat	10	mg/kg/d	Terr. Vert.	Terrestrial animals	Low	TOXLINE
NOAEL	Oral	Chronic	Rat	1	mg/kg/d	Terr. Vert.	Terrestrial animals	Medium	TOXLINE
LD50	Oral	Acute	Rat	169	mg/kg	Terr. Vert.	Mammals: Oral	Medium	TOXLINE
LD50	Oral		Rat	350	mg/kg	Terr. Vert.	Mammals: Oral	Medium	Toxnet
LD50	Oral		Rat	276	mg/kg	Terr. Vert.	Mammals: Oral	Medium	Toxnet
LD50	Oral		Rat	223	mg/kg	Terr. Vert.	Mammals: Oral	Medium	Toxnet
LD50	Oral		Rat	82	mg/kg	Terr. Vert.	Mammals: Oral	Medium	Toxnet
LD50	Oral		Rat	134	mg/kg	Terr. Vert.	Mammals: Oral	Medium	Toxnet
LD50	Dermal		Rabbit	1233	mg/kg	Terr. Vert.	Mammals: Dermal	Medium	Toxnet
LD50	Dermal		Rabbit	>5000	mg/kg	Terr. Vert.	Mammals: Dermal	Low	Toxnet
LD50	Dermal		Rabbit	2000	mg/kg	Terr. Vert.	Mammals: Dermal	Low	Toxnet
LD50	Dermal		Rat	>2000	mg/kg	Terr. Vert.	Mammals: Dermal	Low	Toxnet
LD50	Dermal		Rat	202	mg/kg	Terr. Vert.	Mammals: Dermal	Medium	Toxnet
LD50	Oral		Rock Doves	26.9	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LC50	Oral	5 days	Japanese quail	293	ppm	Terr. Vert.	Avian: Oral	Medium	Toxnet

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor2	Scale	Rank	Reference
LD50	Oral		Japanese quail	15.9	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LD50	Oral		Japanese quail	17.8	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LD50	Oral		Mallard duck	75.6	mg/kg	Terr. Vert.	Avian: Oral	Medium	Toxnet
LD50	Oral		Mallard ducklings	167	mg/kg	Terr. Vert.	Avian: Oral	Medium	Toxnet
LC50	Oral	8 days	Mallard duck	940	mg/L	Terr. Vert.	Avian: Oral	Low	Toxnet
LC50	Dietary	5 days	Northern bobwhite	851.8	mg/kg	Terr. Vert.	Avian: Dietary	Low	Toxnet
LC50	Dietary	28 days	Northern bobwhite	478.5	mg/kg	Terr. Vert.	Avian: Dietary	Medium	Toxnet
LC50	Dietary	28 days	Northern bobwhite	1100	mg/kg	Terr. Vert.	Avian: Dietary	Low	Toxnet
LD50	Oral		Northern bobwhite	32	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LC50	Oral	8 days	Ring necked pheasant	553	ppm	Terr. Vert.	Avian: Oral		Toxnet
LD50	Oral		Pheasant	8.41	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LD50	Oral		Pheasant	17.7	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LD50	Oral		House sparrow	21	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LD50	Oral		Canadian geese	>80	mg/kg	Terr. Vert.	Avian: Oral	Medium	Toxnet

Diflubenzuron (35367-38-5) – growth regulator

Persistence Variables	Value	Units	Rank	Reference
Half-life soil	2	days	Low	Toxnet
Half-life soil	35	days	Low	Toxnet
Half-life water	80	days	Medium	Toxnet
Half-life water	32.5	days	Low	Toxnet
Half-life water	180	days	Medium	Toxnet
Kow	7762	unitless	Medium	Toxnet
Koc	6790	unitless	Medium	Toxnet
Koc	10600	unitless	Medium	Toxnet

Bioaccumulation Variables	Value	Units	Rank	Reference
Log Kow - aquatic	3.89	unitless	Low	Toxnet
BCF - Fish	34	unitless	Low	Toxnet
BCF - Fish	360	unitless	Low	Toxnet
BCF - Fish	78	unitless	Low	Toxnet
Log Kow - terrestrial	3.89	unitless	Medium	Toxnet

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LC50		24 hours	Fairy shrimp	13.3	ug/L	Auatic Invert.	Aquatic invertebrates	Low	Toxnet
LC50		48 hours	Fairy shrimp	0.74	ug/L	Auatic Invert.	Aquatic invertebrates	High	Toxnet
LC50		72 hours	Grass shrimp larvae	2.83	ug/L	Auatic Invert.	Aquatic invertebrates	Medium	Toxnet
LC50		72 hours	Grass shrimp larvae	2.95	ug/L	Auatic Invert.	Aquatic invertebrates	Medium	Toxnet
LC50		96 hours	Opossum shrimp	2.1	ug/L	Auatic Invert.	Aquatic invertebrates	Medium	Toxnet

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LC50		21 days	Opossum shrimp	1.24	ug/L	Auatic Invert.	Aquatic invertebrates	Medium	Toxnet
EC50		48 hours	Water flea	1.5	ug/L	Auatic Invert.	Aquatic invertebrates	Medium	Toxnet
EC50		48 hours	Water flea	3.2	ug/L	Auatic Invert.	Aquatic invertebrates	Medium	Toxnet
EC50		48 hours	Water flea	3.7	ug/L	Auatic Invert.	Aquatic invertebrates	Medium	Toxnet
LC50		Acute	Daphnia magna	7500	ug/L	Auatic Invert.	Aquatic invertebrates	Low	Toxnet
LC50		Acute	Daphnia magna	1700	ug/L	Auatic Invert.	Aquatic invertebrates	Low	Toxnet
LC50			Molluscs	200	mg/L	Auatic Invert.	Aquatic invertebrates	Low	Toxnet
LC50		96 hours	Coho salmon	>150	mg/L	Fish	Fish	Low	Toxnet
LC50		96 hours	Rainbow trout	>150	mg/L	Fish	Fish	Low	Toxnet
LC50		96 hours	Rainbow trout	250	mg/L	Fish	Fish	Low	Toxnet
LC50			Fish	150	mg/L	Fish	Fish	Low	Toxnet
LC50		24 hours	Yellow perch	25	mg/L	Fish	Fish	Low	Toxnet
LC50		96 hours	Yellow perch	25	mg/L	Fish	Fish	Low	Toxnet
LC50		96 hours	Yellow perch	>50	mg/L	Fish	Fish	Low	Toxnet
LC50		96 hours	Channel catfish	370	mg/L	Fish	Fish	Low	Toxnet
LC50		96 hours	Bluegill	660	mg/L	Fish	Fish	Low	Toxnet
Lc50		96 hours	Fathead minnow	430	mg/L	Fish	Fish	Low	Toxnet
LC50		96 hours	Common carp	389	mg/L	Fish	Fish	Low	Toxnet
EC50		72 hours	Green algae	>124000	ug/l	Microalgae	Microorganisms	Low	Toxnet

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
EC50		72 hours	Green algae	>190	ug/l	Microalgae	Microorganisms	Low	Toxnet
EC50		5 days	Diatom	270	ug/L	Microalgae	Microorganisms	Low	Toxnet
EC10			Springtail	19	mg/kg	Terr. Invert	Soil dwelling	Medium	Toxnet
EC10			Enchytraeus crypticus	19	mg/kg	Terr. Invert	Soil dwelling	Medium	Toxnet
LD50			Honeybee	30	ug/bee	Terr. Invert	Non-target insect	Low	Toxnet
LD50			Honeybee	>114.8	ug/bee	Terr. Invert	Non-target insect	Low	Toxnet
LD50	Oral		Rat	>4640	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Mouse	4640	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Rat	10000	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Rabbit	1650	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Mouse	955	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Rat	790	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LC50	Oral		Red winged blackbird	3763	mg/kg	Terr. Vert.	Avian: Oral	Low	Toxnet
LC50	Dietary	8 days	Bobwhite quail	>4640	mg/kg	Terr. Vert.	Avian: Diet	Low	Toxnet
LC50	Dietary	8 days	Bobwhie quail	>20000	mg/kg	Terr. Vert.	Avian: Diet	Low	Toxnet
LC50	Dietary	8 days	Mallard duck	>4640	mg/kg	Terr. Vert.	Avian: Diet	Low	Toxnet
LC50	Dietary	8 days	Mallard duck	>20000	mg/kg	Terr. Vert.	Avian: Diet	Low	Toxnet
LD50	Oral		Mallard duck	>5000	mg/kg	Terr. Vert.	Avian: Oral	Low	Toxnet
LD50	Oral		Norhtern bobwhite quail	>5000	mg/kg	Terr. Vert.	Avian: Oral	Low	Toxnet

Fenthion (55-38-9) - organophosphate

Persistence Variables	Value	Units	Rank	Reference
Half-life soil	34	days	Low	Toxnet
Half-life water	2.9	days	Low	Toxnet
Half-life water	19.7	days	Low	Toxnet
Half-life water	101.7	days	Medium	Toxnet
Kow	12302	unitless	Medium	Toxnet
Koc	1400	unitless	Medium	Toxnet
Koc	4000	unitless	Medium	Toxnet

Bioaccumulation Variables	Value	Units	Rank	Reference
Log Kow - aquatic	4.09	unitless	Medium	Toxnet
BCF - guppies	16600	unitless	High	Toxnet
BCF - Fish	200	unitless	Low	Toxnet
BCF - Fish	760	unitless	Low	Toxnet
BCF - Tadpoles	62	unitless	Low	Toxnet
Log Kow - terrestrial	4.09	unitless	High	Toxnet

Study	Route	Duration	Study2	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LC50		96 hours	Cutthroat trout	1.58	mg/L	Fish	Fish	Medium	Toxnet
LC50		96 hours	Lake trout	1.9	mg/L	Fish	Fish	Medium	Toxnet
LC50		Acute	Poecillia reticulata	0.00212	mg/L	Fish	Fish	High	TOXLINE
LC50		Acute	Cyprinus carpio	0.00253	mg/L	Fish	Fish	High	TOXLINE
LC50		Acute	Tilapia rendalli	0.00292	mg/L	Fish	Fish	High	TOXLINE
LC50		Acute	Oreochromis mossambicus	0.00171	mg/L	Fish	Fish	High	TOXLINE
LC50		96 hours	Coho salmon	1.32	mg/L	Fish	Fish	Medium	Toxnet
LC50		96 hours	Rainbow steelhead trout	0.93	mg/L	Fish	Fish	High	Toxnet
LC50		96 hours	Brown trout	1.33	mg/L	Fish	Fish	Medium	Toxnet

Study	Route	Duration	Study2	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LC50		96 hours	Carp	1.16	mg/L	Fish	Fish	Medium	Toxnet
LD50	Oral		Mouse, albino	160	mg/kg	Terr. Vert.	Mammals: Oral	Medium	TOXLINE
LD50	Oral		Rat, albino	215	mg/kg	Terr. Vert.	Mammals: Oral	Medium	TOXLINE
LD50	Oral		Guinea pig	400	mg/kg	Terr. Vert.	Mammals: Oral	Medium	TOXLINE
LD50	Oral		Rat	190-315	mg/kg	Terr. Vert.	Mammals: Oral	Medium	Toxnet
LD50	Oral		Rat	245-615	mg/kg	Terr. Vert.	Mammals: Oral	Medium	Toxnet
LD50	Oral		Reindeer	105	mg/kg	Terr. Vert.	Mammals: Oral	Medium	TOXLINE
LD50	Oral		Rabbit	150	mg/kg	Terr. Vert.	Mammals: Oral	Medium	Toxnet
LD50	Dermal		Rat	330	mg/kg	Terr. Vert.	Mammals: Dermal	Medium	Toxnet
LD50	Oral		Bobwhite	3.1	mg/kg	Terr. Vert.	Avian: Oral	High	TOXLINE
LD50	Oral		Japanese quail	23	mg/kg	Terr. Vert.	Avian: Oral	High	TOXLINE
LD50	Oral		Mallard duck	5.94	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LD50	Oral		Pheasant	17.8	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LD50	Oral		Chukar	25.9	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LD50	Oral		Japanese quail	10.6	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LD50	Oral		Rock dove	4.63	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LD50	Oral		Mourning dove	2.5	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LD50	Oral		House sparrow	22.7	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LD50	Dietary	5 day	Bobwhite	30	ppm	Terr. Vert.	Avian:Dietary	High	Toxnet
LD50	Dietary	5 day	Japanese quail	86	ppm	Terr. Vert.	Avian:Dietary	High	Toxnet
LD50	Dietary	5 day	Ring necked pheasant	202	ppm	Terr. Vert.	Avian:Dietary	High	Toxnet
LD50	Dietary	5 day	Mallard duck	231	ppm	Terr. Vert.	Avian:Dietary	High	Toxnet
EC50		48 hours	Daphnid	0.62	ug/L	Aquatic Invert.	Aquatic Invert.	High	Toxnet
EC50		48 hours	Daphnid	0.8	ug/L	Aquatic Invert.	Aquatic Invert.	High	Toxnet
EC50		48 hours	Seed shrimp	18	ug/L	Aquatic Invert.	Aquatic Invert.	High	Toxnet
LC50		96 hours	Glass shrimp	10	ug/L	Aquatic Invert.	Aquatic Invert.	High	Toxnet
LC50		Acute	Daphnia pulex	1.3	ug/L	Aquatic Invert.	Aquatic Invert.	High	TOXLINE

Study	Route	Duration	Study2	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LC50		Acute	Ceriodaphnia dubia	1.72	ug/L	Aquatic Invert.	Aquatic Invert.	High	TOXLINE
LC50		96 hours	Sowbugs	1.8	mg/L	Non-target insect	Terr. Invert.	High	Toxnet
LC50		96 hours	Stonefly	0.045	mg/L	Non-target insect	Terr. Invert.	High	Toxnet
LC50		96 hours	Scud	0.0084	mg/L	Non-target insect	Terr. Invert.	High	Toxnet

Methoprene (40596-69-9) – growth regulator (hormonal)

Persistence Variables	Value	Units	Rank	Reference
Half-life soil	10	days	Low	Toxnet
Half-life water	13	days	Low	Toxnet
Half-life water	6.3	days	Low	Toxnet
Half-life water	75	days	Medium	Toxnet
Kow	316227	unitless	High	Toxnet
Koc	23000	unitless	Medium	Toxnet

Bioaccumulation Variables	Value	Units	Rank	Reference
Log Kow - aquatic	5.5	unitless	High	Toxnet
BCF - Aquatic Org.	3400	unitless	Medium	Toxnet
BCF - Fish	75	unitless	Low	Toxnet
BCF - Fish	457	unitless	Low	Toxnet
Log Kow - terrestrial	5.5	unitless	High	Toxnet

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LC50			Bluegill sunfish	4.6	mg/L	Fish	Fish	Medium	PEA2012
LC50			Trout	4.4	mg/L	Fish	Fish	Medium	PEA2012
LC50			Channel catfish; largemouth bass	>100	mg/L	Fish	Fish	Low	PEA2012

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LC50	Oral	96 hours	Bluegill sunfish	4.6	mg/L	Fish	Fish	Medium	Toxnet
LC50	Oral	96 hours	Trout	4.4	mg/L	Fish	Fish	Medium	Toxnet
LC50			Shrimp	>100	mg/L	Aquatic Invert.	Aquatic Invert.	Low	PEA2012
LC50			Estuarine mud crabs	>0.1	mg/L	Aquatic Invert.	Aquatic Invert.	High	PEA2012
EC50		48 hours	Daphnia	0.36	mg/L	Aquatic Invert.	Aquatic Invert.	High	Toxnet
LD50	Oral		Rat	2323	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Mouse	2285	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Rat	>34600	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Dog	5000	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LC50	Dietary	8 days	Chickens	>4640	mg/kg	Terr. Vert.	Avian: Dietary	Low	Toxnet
LD50			Mallard duck	>2000	mg/kg	Terr. Vert.	Avian: Oral	Low	PEA2012
LD50			Chicken	>4640	mg/kg	Terr. Vert.	Avian: Oral	Low	PEA2012
LD50	Dermal		Rabbit	3000	mg/kg	Terr. Vert.	Mammals: Dermal	Low	Toxnet
NOEL			Bobwhite quail	30	ppm	Terr. Vert.	Terrestrial animals	Low	PEA2012
LD50			Honeybee	>1000	ug/bee	Terr. Invert.	Non-target Insects	Low	Toxnet

Novaluron (116714-46-6) – growth regulator

Persistence Variables	Value	Units	Rank	Reference
Half-life soil	4	days	Low	Toxnet
Half-life soil	120	days	Medium	Toxnet
Half-life water	139	days	Medium	Toxnet
Half-life water	101	days	Medium	Toxnet
Kow	186208	unitless	High	Toxnet
Koc	6030	unitless	Medium	Toxnet
Koc	11828	unitless	Medium	Toxnet

Bioaccumulation Variables	Value	Units	Rank	Reference
Log Kow - aquatic	5.27	unitless	High	Toxnet
BCF - Fish	14216	unitless	High	WHO, 2004
BCF - Fish	14645	unitless	High	WHO, 2004
BCF - Tadpoles	15260	unitless	High	Health Canada, 2006
Log Kow - terrestrial	5.27	unitless	High	Toxnet

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
NOAEL	Oral		Rat	1000	mg/kg/d	Terr. Vert.	Mammals: Oral	Low	HSDB
NOAEL	Oral		Rat	8.3	mg/kg/d	Terr. Vert.	Mammals: Oral	Low	HSDB
LD50	Oral	Acute	Rat	>5000	mg/kg/d	Terr. Vert.	Mammals: Oral	Low	WHO, 2004
LD50	Oral	Acute	Mouse	>5000	mg/kg/d	Terr. Vert.	Mammals: Oral	Low	WHO, 2004
LD50	Dermal		Rabbit	non-irritant	mg/kg/d	Terr. Vert.	Mammals: Dermal	Low	WHO, 2004
NOEL			Bobwhite quail	5200	ppm	Terr. Vert.	Terrestrial animals	Low	WHO, 2004
NOEL		Sub-chronic	Bobwhite quail	300	ppm	Terr. Vert.	Terrestrial animals	Low	WHO, 2004
LD50	Oral	Acute	Mallard duck	>2000	mg/kg/d	Terr. Vert.	Avian: Oral	Low	WHO, 2004

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
NOEL	Oral		Mallard duck	2000	mg/kg	Terr. Vert.	Avian: Oral	Low	WHO, 2004
LD50	Oral	Acute	Bobwhite quail	>2000	mg/kg/d	Terr. Vert.	Avian: Oral	Low	WHO, 2004
NOAEL	Oral		Bobwhite quail	2000	mg/kg/d	Terr. Vert.	Avian: Oral	Low	WHO, 2004
LC50	Dietary	Acute	Mallard duck	>5200	ppm	Terr. Vert.	Avian: Dietary	Low	WHO, 2004
NOEL	Dietary	Acute	Mallard duck	5200	ppm	Terr. Vert.	Avian: Dietary	Low	WHO, 2004
NOEL	Dietary	Sub-chronic	Mallard duck	30	ppm	Terr. Vert.	Terrestrial animals	Low	WHO, 2004
LC50	Dietary	Acute	Bobwhite quail	>5200	ppm	Terr. Vert.	Avian: Dietary	Low	WHO, 2004
LC50		Acute	Rainbow trout	>=1	mg/L	Fish	Fish	High	WHO, 2004
LOEC			Rainbow trout	>1	mg/l	Fish	Fish	High	WHO, 2004
LC50		Acute	Carp	>0.744	mg/L	Fish	Fish	High	WHO, 2004
NOEC		Chronic	Rainbow trout	>6.16	ug/L	Fish	Fish	High	WHO, 2004
NOEC			Fathead minnow	0.003	mg/L	Fish	Fish	High	WHO, 2004
EC50		Acute	Daphnia	58	ug/L	Aquatic Invert.	Aquatic Invert.	High	WHO, 2004
EC50		Acute	Daphnia	0.279	ug/L	Aquatic Invert.	Aquatic Invert.	High	WHO, 2004
LC50		Acute	Mayfly	0.032	ug/L	Aquatic Invert.	Aquatic Invert.	High	WHO, 2004
LC50		Acute	Damselfly	0.184	ug/L	Aquatic Invert.	Aquatic Invert.	High	WHO, 2004
NOEC		Acute	Damselfly	0.114	ug/L	Aquatic Invert.	Aquatic Invert.	High	WHO, 2004
LC50		Acute	Lumbriculous variegatus	5	ug/L	Aquatic Invert.	Aquatic Invert.	High	WHO, 2004
NOEC		Acute	Lumbriculous variegatus	5	ug/L	Aquatic Invert.	Aquatic Invert.	High	WHO, 2004
LC50		Acute	Asellus	1.6	ug/L	Aquatic Invert.	Aquatic Invert.	High	WHO, 2004
EC50			Green algae	>9.68	mg/L	Microalgae	Microorganisms	High	WHO, 2004
EC50			Lemna aquatic plant	>777	ug/L	Microalgae	Microorganisms	High	WHO, 2004
LD50			Honeybee	>100	ug/bee	Terr. Invert.	Non-target insects	Low	WHO, 2004
LC50			Earthworm	1000	ppm	Terr. Invert.	Soil dwelling Invertebrates	Low	WHO, 2004

Pirimiphos-methyl (29232-93-7) - organophosphate

Persistence Variables	Value	Units	Rank	Reference
Half-life soil	5.2	days	Low	Toxnet
Half-life soil	5.9	days	Low	Toxnet
Half-life water	7.3	days	Low	Toxnet
Half-life water	79	days	Medium	Toxnet
Kow	13182	unitless	Medium	Toxnet
Koc	950	unitless	Medium	Toxnet
Koc	8500	unitless	Medium	Toxnet

Bioaccumulation Variables	Value	Units	Rank	Reference
Log Kow-aquatic	4.12	unitless	Medium	Toxnet
Log Kow-soil	4.12	unitless	High	Toxnet
BCF - Fish	270	unitless	Low	Toxnet

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LD50	Dermal		Honeybee	11.6	ug/bee	Terr. Invert.	Non-target insect	Low	Toxnet
LD50	Dermal		Honeybee	0.0666	ug/bee	Terr. Invert.	Non-target insect	High	Toxnet
LD50	Dermal		Honeybee	0.39	ug/bee	Terr. Invert.	Non-target insect	High	Toxnet
LD50	Oral		Honeybee	0.36	ug/bee	Terr. Invert.	Non-target insect	High	Toxnet
LC50			Snail	6	mg/L	Terr. Invert.	Soil dwelling Org.	High	Toxnet
LC50			Flatworm	2.6	mg/L	Terr. Invert.	Soil dwelling Org.	High	Toxnet
NOAEL			Beagle	2	mg/kg/d	Terr. Vert.	Terrestrial animals	Medium	HSDB
NOAEL			Rat	0.4	mg/kg/d	Terr. Vert.	Terrestrial animals	Medium	HSDB
NOAEL			Rat	25	mg/kg/d	Terr. Vert.	Terrestrial animals	Low	HSDB
LC50			Rat, Mouse	2050	mg/kg	Terr. Vert.	Mammals: Oral	Low	TOXLINE

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LD50	Oral		Rat	1250	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Mouse	1180	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Rabbit	1150	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Guinea pig	1000	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Rat	1450	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Rat	1840-2260	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Mouse	1030-1360	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Guinea pig	1000-2000	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
ID50	Oral		Rabbit	1154-2300	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Dog	1500	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Cat	575-1150	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Dermal		Rat	2000	mg/kg	Terr. Vert.	Mammals: Dermal	Low	Toxnet
LC50	Deitary	8 days	Northern Bobwhite quail	298	ppm	Terr. Vert.	Avian: Dietary	Low	Toxnet
LC50	Dietary	8 days	Northern Bobwhite quail	207	ppm	Terr. Vert.	Avian: Dietary	Low	Toxnet
LC50	Dietary	8 days	Mallard duck	633	ppm	Terr. Vert.	Avian: Dietary	Low	Toxnet
LD50	Oral	14 days	Bobwhite quail	5.46	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LD50	Oral	14 days	Mallard duck	10.4	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LD50	Oral		Hen	30-60	mg/kg	Terr. Vert.	Avian: Oral	High	Toxnet
LC50		1 hour	Eastern rainbow fish	0.015	mg/L	Fish	Fish	High	Toxnet
LC50		96 hours	Bluegill	2.86	mg/L	Fish	Fish	Medium	Toxnet
LC50		96 hours	Fathead minnow	2.5	mg/L	Fish	Fish	Medium	Toxnet
LC50		24 hours	Guppy	4.6	mg/L	Fish	Fish	Medium	Toxnet
LC50		48 hours	Common carp	5	mg/L	Fish	Fish	Medium	Toxnet
LC50		96 hours	Rainbow trout	1.16	mg/L	Fish	Fish	Medium	Toxnet
LC50		96 hours	Rainbow trout	0.404	mg/L	Fish	Fish	High	Toxnet
LC50		48 hours	Rainbow trout	1	mg/L	Fish	Fish	High	Toxnet
LC50		24 hours	Western mosquitofish	0.033	mg/L	Fish	Fish	High	Toxnet

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LC50			Common carp	5	mg/L	Fish	Fish	Medium	HSDB
LC50			Guppy	0.019	ml/L	Fish	Fish	High	TOXLINE
LC50			Algae	956	mg/L	Microalgae	Microorganisms	Low	HSDB
LC50			Algae	21.7	mg/L	Microalgae	Microorganisms	Medium	HSDB
LC50		120 hours	Green algae	264	mg/L	Microalgae	Microorganisms	Low	Toxnet
LC50		48 hours	Green algae	956	mg/L	Microalgae	Microorganisms	Low	Toxnet
LC50		120 hours	Green algae	217	mg/L	Microalgae	Microorganisms	Low	Toxnet
EC50		48 hours	Daphnia magna	0.11	ug/L	Aquatic Invert.	Aquatic Invert.	High	Toxnet
EC50		48 hours	Daphnia larvae	0.21	ug/L	Aquatic Invert.	Aquatic Invert.	High	Toxnet
EC50		48 hours	Daphnia magna	0.44	ug/L	Aquatic Invert.	Aquatic Invert.	High	Toxnet
EC50		48 hours	Daphnia magna	0.17	ug/L	Aquatic Invert.	Aquatic Invert.	High	Toxnet
LC50			Scud	18.32	ug/L	Aquatic Invert.	Aquatic Invert.	High	Toxnet
LC50			Scud shrimp	5.49	ug/L	Aquatic Invert.	Aquatic Invert.	High	HSDB

Pyriproxyfen (122453-73-0) – pyridine-based pesticide

Persistence Variables	Value	Units	Rank	Reference
Half-life soil	12.4	days	Low	Sullivan, 2000
Half-life soil	14.5	days	Low	Kollman, 1995
Half-life soil	6.4	days	Low	Sullivan, 2000
Half-life soil	9	days	Low	Sullivan, 2000
Half-life soil	36	days	Low	Sullivan, 2000
Half-life water	7.5	days	Low	Toxnet
Half-life water	1.6	days	Low	UH PPDB, 2016
Half-life sediment	6.5	days	Low	UH PPDB, 2016
Kow	236000	unitless	High	Sullivan, 2000
Kow	234000	unitless	High	UH PPDB, 2016
Koc	405000	unitless	High	Toxnet

Bioaccumulation Variables	Value	Units	Rank	Reference
Log Kow - aquatic	5.6	unitless	High	Toxnet
Log Kow - terrestrial	5.6	unitless	High	Toxnet
BCF - Fish	3700	unitless	Medium	Toxnet
BCF - Fish	660	unitless	Low	EFSA, 2009
BCF - Fish	1379	unitless	Medium	UH PPDB, 2016

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LD50	Oral		Rat	>5000	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Dermal		Rabbit	>2000	mg/kg	Terr. Vert.	Mammals: Dermal	Low	Toxnet
LD50		Acute	Birds	>1906	mg/kg	Terr. Vert.	Avian: Oral	Low	UH PPDB, 2016
LC50		Acute	Birds	>863	mg/kg	Terr. Vert.	Avian: Oral	Low	UH PPDB, 2016
LD50	Oral	Acute	Mallard duck	>2000	mg/kg	Terr. Vert.	Avian: Oral	Low	Sullivan, 2000
LD50	Oral	Acute	Bobwhite quail	>2000	mg/kg	Terr. Vert.	Avian: Oral	Low	Sullivan, 2000
LD50	Dietary		Mallard duck	>5200	ppm	Terr. Vert.	Avian: Dietary	Low	Sullivan, 2000
LD50	Dietary		Bobwhite quail	>5200	ppm	Terr. Vert.	Avian: Dietary	Low	Sullivan, 2000
NOAEL		Chronic	Mouse	600	ppm	Terr. Vert.	Terrestrial Animals	Low	Toxnet
NOAEL		Chronic	Rat	35.1	ppm	Terr. Vert.	Terrestrial Animals	Low	Toxnet
LC50		96 hours	Bluegill sunfish	0.27	mg/L	Fish	Fish	High	Sullivan, 2000
LC50		96 hours	Rainbow trout	0.325	mg/L	Fish	Fish	High	Sullivan, 2000
LC50		21 day	Rainbow trout	0.09	mg/L	Fish	Fish	High	Sullivan, 2000
LC50		96 hours	Carp	0.45	mg/L	Fish	Fish	High	Sullivan, 2000
LC50		96 hours	Killfish	2.66	mg/L	Fish	Fish	Medium	Sullivan, 2000
EC50		Acute	Algae	0.15	mg/L	Microalgae	Microorganisms	High	UH PPDB, 2016
EC50		Acute	Aquatic plants	>0.18	mg/L	Microalgae	Microorganisms	High	UH PPDB, 2016
LD50	Dermal		Honeybee	74	ug/bee	Terr. Invert.	Non-target insects	Low	UH PPDB, 2016
LD50	Oral		Honeybee	>100	ug/bee	Terr. Invert.	Non-target insects	Low	UH PPDB, 2016

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LC50	Dermal		Honeybee	>100	ug/bee	Terr. Invert.	Non-target insects	Low	Sullivan, 2000
LC50		Acute	Earthworm	>500		Terr. Invert.	Soil dwelling invert.	Low	UH PPDB, 2016
EC50			Aquatic invert.	0.4	mg/L	Aquatic Invert.	Aquatic Invert.	High	UH PPDB, 2016
EC50		48 hours	Daphnia magna	0.4	mg/L	Aquatic Invert.	Aquatic Invert.	High	Sullivan, 2000
LC50			Daphnia	0.08	ppm	Aquatic Invert.	Aquatic Org.	High	Toxnet
LC50			Shrimp	0.098	ppm	Aquatic Invert.	Aquatic Org.	High	Toxnet
LD50		96 hours	Mysid shrimp	0.092	mg/L	Aquatic Invert.	Aquatic Org.	High	Sullivan, 2000

Spinosad (A: 131929-60-7, D: 131929-63-0) – bacterial-produced insecticide

Persistence Variables	Value	Units	Rank	Reference
Half-life soil	8.68	days	Low	Toxnet
Half-life soil	9.44	days	Low	Toxnet
Half-life soil	9	days	Low	AMS, 2002
Half-life soil	17	days	Low	AMS, 2002
Half-life water	>30	days	Low	Toxnet
Kow	54.6	unitless	Low	Kollman, 1995
Kow	90	unitless	Low	Kollman, 1995
Koc	35838	unitless	High	Kollman, 1995

Bioaccumulation Variables	Value	Units	Rank	Reference
Log Kow - aquatic	4.1	unitless	Medium	Toxnet
Log Kow - terrestrial	4.1	unitless	High	Toxnet
Log Kow - aquatic	4.01	unitless	Medium	Toxnet
Log Kow - terrestrial	4.01	unitless	High	Toxnet

Bioaccumulation Variables	Value	Units	Rank	Reference
BCF - Fish	33	unitless	Low	Dow, 2001
BCF - Fish	33	unitless	Low	Dow, 2001

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LD50	Oral		Rat	3738	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Oral		Rat	>5000	mg/kg	Terr. Vert.	Mammals: Oral	Low	Toxnet
LD50	Dermal		Rabbit	>2000	mg/kg	Terr. Vert.	Mammals: Dermal	Low	Toxnet
LD50	Oral		Mallard duck	>1333	mg/kg	Terr. Vert.	Avian: Oral	Low	Toxnet
LD50			Mallard duck	5253	mg/kg	Terr. Vert.	Avian: Oral	Low	Thompson, 2000
LD50	Oral		Northern bobwhite quail	>1333	mg/kg	Terr. Vert.	Avian: Oral	Low	Toxnet
NOAEL			Rat	8.2	mg/kg/day	Terr. Vert.	Terrestrial Animals	Low	HSDB, 2009
NOAEL			Mouse	7.5	mg/kg/day	Terr. Vert.	Terrestrial Animals	Low	HSDB, 2009
NOAEL			Mouse	11.4	mg/kg/day	Terr. Vert.	Terrestrial Animals	Low	HSDB, 2009
NOAEL			Rabbit	1000	mg/kg/day	Terr. Vert.	Terrestrial Animals	Low	HSDB, 2009
NOAEL			Dog	4.9	mg/kg/day	Terr. Vert.	Terrestrial Animals	Medium	HSDB, 2009
NOAEL			Dog	2.7	mg/kg/day	Terr. Vert.	Terrestrial Animals	Medium	HSDB, 2009
NOAEL			Rat	2.4	mg/kg/day	Terr. Vert.	Terrestrial Animals	Medium	HSDB, 2009
LD50		48 hours	Honeybee	0.0029	ug/bee	Terr. Invert.	Non-target insects	High	Toxnet
LC50		96 hours	Rainbow trout	30	ppm	Fish	Fish	Low	Toxnet
LC50			Carp	5	ppm	Fish	Fish	Medium	Kollman, 1995
LC50		96 hours	Bluegill sunfish	5.94	ppm	Fish	Fish	Medium	Toxnet
LC50		96 hours	Sheepshead minnow	7.87	ppm	Fish	Fish	Medium	Toxnet
LC50			Daphnia	7.9	ppm	Aquatic Invert.	Aquatic Org.	Medium	Dow, 2001

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LC50		96 hours	Grass shrimp	>9.76	ppm	Aquatic Invert.	Aquatic Org.	Medium	Toxnet
EC50			Eastern oyster	0.295	ppm	Aquatic Invert.	Aquatic Invert.	High	Dow, 2001
EC50			Green algae	>105.5	ppm	Microalgae	Microorganisms	Low	Kollman, 1995
EC50			Freshwater diatom	0.107	ppm	Microalgae	Microorganisms	High	Kollman, 1995
EC50			Duckweed	10.6	ppm	Microalgae	Microorganisms	Medium	Kollman, 1995

Temephos (3383-96-8) **– organophosphate**

Persistence Variables	Value	Units	Rank	Reference
Half-life soil	30	days	Low	Toxnet
Half-life water	400	days	High	Toxnet
Half-life water	106	days	Medium	Toxnet
Kow	912010	unitless	High	Toxnet
Koc	18250	unitless	Medium	Toxnet
Koc	31800	unitless	Medium	Toxnet

Bioaccumulation Variables	Value	Units	Rank	Reference
Log Kow - aquatic	5.96	unitless	High	Toxnet
BCF - Fish	2300	unitless	Medium	Toxnet
Log Kow - terrestrial	5.96	unitless	High	Toxnet

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LD50			Quail	18.9	mg/kg	Terr. Vert.	Avian: Oral	High	PEA2012
LD50	Oral		Chukar partridge	240	mg/kg	Terr. Vert.	Avian: Oral	Medium	Toxnet
LD50	Oral		Rock dove	50.1	mg/kg	Terr. Vert.	Avian: Oral	Medium	Toxnet
LD50	Oral		House sparrow	35.4	mg/kg	Terr. Vert.	Avian: Oral	Medium	Toxnet

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LD50	Oral		Hen	183	mg/kg	Terr. Vert	Avian: Oral	Medium	Toxnet
LD50	Oral		Mallard duck	79.4	mg/kg	Terr. Vert	Avian: Oral	Medium	Toxnet
LD50	Oral		Mallard duck	31.5	ppm	Terr. Vert	Avian: Oral	High	Toxnet
LD50	Oral		Bobwhite quail	27.4	mg/kg	Terr. Vert	Avian: Oral	High	Toxnet
LD50	Oral		Pheasant	35.4	mg/kg	Terr. Vert	Avian: Oral	High	Toxnet
LD50	Oral		Japanese quail	84.1	mg/kg	Terr. Vert	Avian: Oral	Medium	Toxnet
LC50	Dietary	5 days	Mallard duck	894	ppm	Terr. Vert	Avian: Dietary	Medium	Toxnet
LC50	Dietary	5 days	Bobwhite quail	92	ppm	Terr. Vert	Avian: Dietary	High	Toxnet
LC50	Dietary	5 days	Pheasant	162	ppm	Terr. Vert	Avian: Dietary	High	Toxnet
LC50	Dietary	5 days	Japanese quail	260	ppm	Terr. Vert.	Avian: Dietary	High	Toxnet
LC50	Dietary	5 days	Japanese quail	288	ppm	Terr. Vert.	Avian: Dietary	High	Toxnet
LC50	Dietary	5 days	House sparrow	47	ppm	Terr. Vert.	Avian: Dietary	High	Toxnet
LD50	Dermal		Rabbit	970	mg/kg	Terr. Vert	Mammals: Dermal	Medium	Toxnet
LD50	Dermal		Rabbit	1930	mg/kg	Terr. Vert	Mammals: Dermal	Medium	Toxnet
LD50	Dermal		Rat	>4000	mg/kg	Terr. Vert	Mammals: Dermal	Low	Toxnet
LD50	Dermal		Rat	1370	mg/kg	Terr. Vert	Mammals: Dermal	Medium	Toxnet
LD50	Dermal		Rabbit	970	mg/kg	Terr. Vert	Mammals: Dermal	Medium	Toxnet
LD50	Oral		Rat	8600	mg/kg	Terr. Vert	Mammals: Oral	Low	Toxnet
LD50	Oral		Rat	13000	mg/kg	Terr. Vert	Mammals: Oral	Low	Toxnet
LD50	Oral		Rat	444	mg/kg	Terr. Vert	Mammals: Oral	Medium	Toxnet
LD50	Oral		Rat	1000	mg/kg	Terr. Vert	Mammals: Oral	Low	Toxnet
LD50	Oral		Mouse	223	mg/kg	Terr. Vert	Mammals: Oral	Medium	Toxnet
LD50	Oral		Rabbit	313	mg/kg	Terr. Vert	Mammals: Oral	Medium	Toxnet
EC50		48 hours	Daphnia magna	0.011	ug/L	Aquatic Invert.	Aquatic Invert.	High	Toxnet
LC50		24 hours	Salamandar larvae	3.97	mg/L	Aquatic Invert.	Aguatic Org.	Medium	Toxnet

Study	Route	Duration	Eco Receptor	Benchmark	Units	Eco Receptor Category	Scale	Rank	Reference
LC50		24 hours	Frog larvae	4.18	mg/L	Aquatic Invert.	Aguatic Org.	Medium	Toxnet
LC50		24 hours	Mosquitofish larvae	0.0056	mg/L	Aquatic Invert.	Aguatic Org.	High	Toxnet
LC50		48 hours	Mosquitofish larvae	0.00411	mg/L	Aquatic Invert.	Aguatic Org.	High	Toxnet
LC50		96 hours	Scud	0.08	mg/kg	Aquatic Invert.	Aguatic Org.	High	Toxnet
LC50			Pink shrimp	0.005	mg/L	Aquatic Invert.	Aguatic Org.	High	PEA2012
LC50			Eastern oyster	0.019	mg/L	Aquatic Invert.	Aguatic Org.	High	PEA2012
LC50		24 hours	Western mosquitofish	0.003	mg/L	Fish	Fish	High	Toxnet
LC50		24 hours	Bluegill	8.7	mg/L	Fish	Fish	Medium	Toxnet
LC50		24 hours	Bluegill	11.5	mg/L	Fish	Fish	Low	Toxnet
LC50		24 hours	Bluegill	4.27	mg/L	Fish	Fish	Medium	Toxnet
LC50		24 hours	Bluegill	54	mg/L	Fish	Fish	Low	Toxnet
LC50		24 hours	Rainbow trout	13.1	mg/L	Fish	Fish	Low	Toxnet
LC50		24 hours	Rainbow trout	1.42	mg/L	Fish	Fish	Medium	Toxnet
LC50		24 hours	Rainbow trout	1.7	mg/L	Fish	Fish	Medium	Toxnet
LC50		24 hours	Rainbow trout	2.79	mg/L	Fish	Fish	Medium	Toxnet
LC50		96 hours	Coho salmon	0.35	mg/L	Fish	Fish	High	Toxnet
LC50		96 hours	Largemouth bass	1.44	mg/L	Fish	Fish	Medium	Toxnet
LC50		96 hours	Largemouth bass	2.21	mg/L	Fish	Fish	Medium	Toxnet
LC50		96 hours	Largemouth bass	3.06	mg/L	Fish	Fish	Medium	Toxnet
LC50		96 hours	Largemouth bass	4.14	mg/L	Fish	Fish	Medium	Toxnet
LC50		24 hours	Channel catfish	5-7	mg/L	Fish	Fish	Medium	Toxnet
LC50		24 hours	Channel catfish	>10	mg/L	Fish	Fish	Low	Toxnet
LC50		24 hours	Channel catfish	>18	mg/L	Fish	Fish	Low	Toxnet
LC50		24 hours	Channel catfish	>21	mg/L	Fish	Fish	Low	Toxnet
LD50			Honeybee	1.55	ug/bee	Terr. Invert.	Non-target insect	High	Toxnet

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ANNEX E. PESTICIDE USE AND TOXICOLOGICAL PROFILES

PROFILE FOR ALPHA-CYPERMETHRIN:

CAS REGISTRY NUMBER 67375-30-8

SUMMARY OF INSECTICIDE

CHEMICAL HISTORY

Alpha-cypermethrin is a highly active synthetic pyrethroid insecticide used to control a wide variety of pests in agricultural and public health applications. It is similar to the natural insecticide pyrethrum, which comes from chrysanthemums; however, it is more effective and longer lasting (ATSDR, 2003; IPCS, 1992). Alpha-cypermethrin is available in technical grade formulation, emulsifiable concentrate, ultra-low-volume formulation, suspension concentrate, and in mixtures with other insecticides (HSDB, 2005; IPCS, 1992). For mosquito control, it is used in bed nets and other materials that are dipped in alpha-cypermethrin to protect the user (WHO, 1997, 1998). It is considered one of the best insecticides for impregnation of traps and screens (WHO, 1997). Alpha-cypermethrin is not currently registered for use in the United States (HSDB, 2005), but cypermethrin is.

Alpha-cypermethrin is of low risk to humans when used at levels recommended for its designed purpose (HSDB, 2005; ATSDR, 2003). However, as a synthetic pyrethroid, alpha-cypermethrin exhibits its toxic effects by interfering with the way the nerves and brain normally function (HSDB, 2005; ATSDR, 2003). It has moderate acute toxicity and is a suspected endocrine disruptor but does not inhibit cholinesterase (PAN, 2005). Typical symptoms of acute exposure are irritation of skin and eyes, headaches, dizziness, nausea, vomiting, diarrhea, and excessive salivation and fatigue. Inhaled alpha-cypermethrin has been shown to cause cutaneous paraesthesias or a burning, tingling, or stinging. However, these effects are generally reversible and disappear within a day of removal from exposure (HSDB, 2005; ATSDR, 2003; PAN, 2005). Alpha-cypermethrin is harmful if swallowed (MSDS, n.d.). Inhalation and dermal exposure are the most likely human exposure routes (HSDB, 2005). Environmental levels of significance are unlikely if alpha-cypermethrin is applied at recommended rates (IPCS, 1992).

DESCRIPTION OF DATA QUALITY AND QUANTITY

Comprehensive reviews on the toxicity of alpha-cypermethrin are not widely available but include the following:

- Toxicological Profile for Pyrethrin and Pyrethroids (ATSDR, 2003)
- Environmental Health Criteria 142: Alpha- Cypermethrin (IPCS, 1992)

EPA and ATSDR have developed quantitative oral human health benchmarks (EPA's chronic RfD and ATSDR's acute oral MRL) for cypermethrin. Alpha-cypermethrin makes up one quarter of the racemic mixture cypermethrin and has a similar mode of action. Alpha-cypermethrin is also similar to cypermethrin with regard to the signs of intoxication, target organs effects, and metabolic pathways (IPCS, 1992).

SUMMARY TABLE

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute, Intermediate, Chronic	Inhalation	4	mg/kg/day	Inhalation NOAEL in rats with UF of 100 applied	

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute	Oral	0.02	mg/kg/day	Acute oral MRL for cypermethrin based on neurological effects in rats with UF of 1000 applied	ATSDR (2003)
Intermediate	Oral	0.01	mg/kg/day	Adopt chronic RfD as intermediate duration	
Chronic	Oral	0.01	mg/kg/day	Chronic oral RfD for cypermethrin based on neurological effects in dogs with UF of 100 applied	U.S. EPA (2005)
Acute, Intermediate, Chronic	Dermal	5	mg/kg/day	Dermal NOAEL in rats with UF of 100 applied	

For inhalation exposure, a NOAEL of 400 mg/m^3 (447 mg/kg/day)[1] was identified for neurological and respiratory effects in rats exposed to alpha-cypermethrin via inhalation for 4 hours (IPCS, 1992). An uncertainty factor of 100 to account for intra- and interspecies variation was applied, for an inhalation benchmark of 4 mg/kg/day. This value is appropriate for all exposure durations.

Due to limited low-dose oral data for alpha-cypermethrin, health benchmarks for cypermethrin were used and are expected to be protective of human health. The acute oral MRL for cypermethrin of 0.02 mg/kg/day is based on a LOAEL of 20 mg/kg for neurological effects (altered gait and decreased motor activity) in rats with an uncertainty factor of 1,000 applied. Long-Evans rats were given single gavage doses of up to 120 mg/kg cypermethrin. Motor activity and FOB were assessed at 2 and 4 hours post-dosing. A NOAEL was not identified (ATSDR, 2003). The chronic oral RfD for cypermethrin of 0.01 mg/kg/day is based on a NOEL of 1 mg/kg/day for systemic effects with an uncertainty factor of 100 applied. Beagle dogs were dosed with up to 15 mg/kg/day cypermethrin in corn oil for 52 weeks. During the first week, increased vomiting was observed in dogs at all dose levels. Additionally, throughout the study all dogs passed liquid feces; however, the incidence was 10- and 30-fold higher in the 5 and 15 mg/kg/day groups, respectively. The NOEL identified for this study was 1 mg/kg/day (U.S. EPA, 2005).

For dermal exposure, a NOAEL of 500 mg/kg/day was identified in rats dermally exposed to alpha-cypermethrin once for 24 hours (IPCS, 1992). An uncertainty factor of 100 to account for intra- and interspecies variation was applied, for a dermal benchmark value of 5 mg/kg/day. This value is appropriate for all exposure durations.

Insecticide Background

CASRN: 67375-30-8

Synonyms: alfamethrin, alphamethrin, alphacypermethrin, alpha-cypermethrin, alfa-cipermetrina, alfacypermetrin, alfa cipremetrin,[1alpha(S*),3alpha]-(+ -)-Cyano(3-

[1] Conversion between mg/m^3 and mg/kg/day assumes, for Fischer-344 rats, an average body weight of 0.152 kg and inhalation rate of 0.17 m^3/day (U.S. EPA, 1988).

	phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)- 2,2-dimethylcyclopropanecarboxylate, (1R cis S) and (1S cis R) Enantiomeric isomer pair of alpha-cyano-3- phenoxybenzyl-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylate, Pesticide Code 209600(S)-alpha-cyano-3-phenoxybenzyl-(1R)-cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (R)-alpha-cyano-3-phenoxybenzyl-(1S)-cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate, WL 85871, cyano(3-phenoxyphenyl)methyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (+)-cis isomer, alphametrin, numerous other systematic and non-systematic names (HSDB, 2005; PAN 2005; ATSDR, 2003; MSDS, n.d.)
Chemical Group:	pyrethroid (PAN, 2005)
Registered Trade Names:	Bestox, Fastac, Concord, Dominex, Fendona, Fendona 1.5 SC, Fendona 10 SC, Fendonal WP, Renegade (HSDB, 2005, IPCS, 1992, WHO, 2002), Tenopa SC (alphacypermethrin + flufenoxuron) (HSDB, 2005; PAN 2005; ATSDR, 2003; MSDS, n.d.)

USAGE

Alpha-cypermethrin is a pyrethroid insecticide used to combat a wide variety of chewing and sucking insects on field crops, fruits and vegetables, and in forestry uses. It may be applied to crops as either a curative or preventative treatment. Alpha-cypermethrin is also used in public health applications to control mosquitoes, flies, and other pests. For animal husbandry it is used as an ectoparaciticide and to control flies (HSDB, 2005; IPCS, 1992). Alpha-cypermethrin belongs to the pyrethroid class of insecticides, which have long been used to control mosquitoes, human lice, beetles, and flies (ATSDR, 2003). For mosquito protection, it is used in bed nets and other materials that are dipped into the alpha-cypermethrin to protect the user. Alpha-cypermethrin has been available since 1983 (IPCS, 1992); however, it not currently registered for use in the United States (HSDB, 2005).

FORMULATIONS AND CONCENTRATIONS

Alpha-cypermethrin is available in technical grade, emulsifiable concentrates, wettable powder, suspension concentrates, ultra-low-volume liquids, tablets, and in mixtures with other insecticides (HSDB, 2005; IPCS, 1992). Technical grade alpha-cypermethrin is greater than 90 percent pure (HSDB, 2005). Common formulations of alpha-cypermethrin include Fastac, which is available as an emulsifiable concentrate (20–100 g/L), a wettable powder (50 g/kg), a suspension concentrate (15–250 g/L), and an ultra-low-volume liquid (6–15 g/L); and Fendona and Renegade, which are available as an emulsifiable concentrate (50 or 100 g/L), a suspension concentrate (250 g/L), and a wettable powder (50 g/kg). Alpha-cypermethrin is combined with other active ingredients to form other products (IPCS, 1992). WHO has indicated that the content of alpha-cypermethrin in the formulated products must be declared and shall not exceed the listed standards. Technical grade alpha-cypermethrin must have no less than 910 g/kg alphacypermethrin cis 2 ([IR cis] S and [IS cis] R isomers), and the combined content of the cis and trans isomers of alpha-cyano-3-phenoxybenzyl-2,2-dimethyl-3-(2,2-dichlorovinyl-) cyclopropanecarboxylate must be at least 975 g/kg. No more than 1 g/kg of volatile hydrocarbon solvent and 1 mg/kg of triethylamine is permitted. The aqueous suspension concentrate should contain alphacypermethrin cis 2 ([IR cis] S and [IS cis] R isomers) as follows: up to 25

g/kg, ± 15 percent of the declared content; 25 to 100 g/kg, ± 10 percent of the declared content. The alphacypermethrin cis 1:cis 2 isomer ratio must be lower than 5:95 (WHO, 1999).

SHELF LIFE

Alpha-cypermethrin is stable in acidic and neutral environments. However, it hydrolyses at pH 12–13 and decomposes at temperatures greater than 220 °C. For practical purposes, field studies have indicated that it is stable to sunlight (IPCS, 1992). It is not compatible with strong oxidizing agents (MSDS, n.d.).

DEGRADATION PRODUCTS

Based on its structure, alpha-cypermethrin is expected to readily biodegrade in the environment. However, in two tests it did not degrade and therefore cannot be considered readily biodegradable. One of the major transformation products in the microbial transformation of technical alpha-cypermethrin is 3-phenoxybenzoic acid, which is then transformed to 4-hydroxy-3-phenoxybenzoic acid (IPCS, 1992).

ENVIRONMENTAL BEHAVIOR

FATE AND TRANSPORT IN TERRESTRIAL SYSTEMS

Based on its Koc value, alpha-cypermethrin binds tightly to soil, making it almost immobile in most soil types. In moist soil, volatilization is expected to be the major fate process; however its bond to soil lessens this effect. Volatilization is not a major fate process for dry soil. Biodegradation by environmental organisms in non-sterile soil and by sunlight is expected (HSDB, 2005; IPCS, 1992). Studies have shown that within 2 weeks of treatment with 0.5 kg ai/ha (active ingredient per hectare) of a diluted alpha-cypermethrin emulsifiable concentrate formulation in sandy-clay soil, residues of alpha-cypermethrin were 50 percent less. After 1 year, they were below detection or < 0.01 mg/kg. Similar results were seen after a second and third application to the site indicating that alpha-cypermethrin did not build up in the surface soil. Additionally, no leaching to subsurface soils was observed. Alpha-cypermethrin also does not build up in peat soils (IPCS, 1992).

FATE AND TRANSPORT IN AQUATIC SYSTEMS

Alpha-cypermethrin binds tightly to suspended solids and sediments in water. It is expected to volatilize from water; however, volatilization is lessened by alpha-cypermethrin's bond with soil. Reported volatilization half-lives are 8 days for a river models and 65 days for a lake model. If adsorption is taken into consideration, the estimated volatilization half-life in a pond model is 125 years. Estimated hydrolysis half-lives are 36 and 4 years at pH 7 and 8 respectively. Alpha-cypermethrin is also expected to undergo photodecomposition. Based on its bioconcentration factor, alpha-cypermethrin has a high potential to bioconcentrate in aquatic organism; however, its potential may actually be lower than this suggests because of the ability of aquatic organisms to rapidly metabolize alpha-cypermethrin (HSDB, 2005).

HUMAN HEALTH EFFECTS

ACUTE EXPOSURE

Effects/Symptoms

Limited data exist on the acute toxicity of alpha-cypermethrin in humans (IPCS, 1992; HSDB, 2005). Occupationally exposed workers reported only mild skin irritation (IPCS, 1992). The main effects reported from acute exposure to alpha-cypermethrin in humans include skin rashes, eye irritation, itching and burning sensation on exposed skin, and paraesthesia. Acute inhalation exposures may cause upper and lower

respiratory tract irritation. Ingestion of alpha-cypermethrin is also harmful (HSDB, 2005; MSDS, n.d.). No acute poisonings have been reported (IPCS, 1992).

In rodents, alpha-cypermethrin has moderate to high oral toxicity (HSDB, 2005; IPCS, 1992). Oral LD_{50} values in rats and mice vary greatly and depend on the formulation, concentration, and the vehicle (IPCS, 1992). Acute oral LD_{50} values for technical alpha-cypermethrin range from 79 to 400 mg/kg (in corn oil) in rats (HSDB, 2005; IPCS, 1992; MSDS, n.d.). Although the LD_{50} of 80 mg/kg is considered representative, higher values have been reported. In mice, the reported acute oral LD_{50} of technical alpha-cypermethrin is 35 mg/kg (in corn oil). Oral LD_{50} values for formulated alpha-cypermethrin in rats range from 101 to 174 mg/kg for an emulsifiable concentrate formulation (100 g/L), while 1,804 mg/kg was reported for a suspension concentrate formulation (100 mg/L) and 5,838 mg/kg for an ultra-low-volume liquid formulation (15 g/L) (IPCS, 1992). Clinical signs reported in orally exposed animals are associated with central nervous system activity and included ataxia; gait abnormalities; choreoathetosis; "tip-toe" walk; and increased salivation, lacrimation, piloerection, tremor, and clonic convulsions. Acute dermal exposures are minimally irritating to the skin and eyes of rabbit skin. However, some formulations can cause severe eye irritation that includes corneal opacity and iris damage. Stimulation of the sensory-nerve endings of the skin has been observed in guinea pigs. Reported dermal LD_{50} values of greater than 2,000 mg tech/kg are reported for rats and rabbits (HSDB, 2005; IPCS, 1992). No mortality or signs of toxicity were observed in rats or mice after single dermal applications of up to 500 mg/kg or 4-hour inhalation exposure of mice to 400 mg/m^3. Alpha-cypermethrin is not a dermal sensitizer in guinea pigs (IPCS, 1992).

TREATMENT

Pyrethroid insecticides and their metabolites can be detected in blood and urine; however, the methods are not practical to use given how quickly these compounds are broken down in the body (ATSDR, 2003). Alpha-cypermethrin poisoning should be treated the same as a pyrethroid poisoning. There are no antidotes for alpha-cypermethrin exposure. Treatment is supportive and depends on the symptoms of the exposed person. Decontamination is all that is necessary for most exposures. If a person exhibits signs of typical pyrethroid toxicity following alpha-cypermethrin exposure (nausea, vomiting, shortness of breath, tremors, hypersensitivity, weakness, burning, or itching), they should immediately remove any contaminated clothing. Any liquid contaminant on the skin should be soaked up and the affected skin areas cleaned with alkaline soap and warm water. The application of topical vitamin E helps to relieve the symptoms of paraesthesia. Eye exposures should be treated by rinsing with copious amounts of saline or room temperature water for at least 15 minutes. Contact lenses should be removed. Medical attention should be sought if irritation, pain, swelling, lacrimation, or photophobia persists. The treatment of ingestion exposures is mostly symptomatic and supportive. Care should be taken to monitor for the development of hypersensitivity reactions with respiratory distress. Gastric decontamination is recommended if large amounts have been very recently ingested, and oral administration of activated charcoal and cathartic are recommend for ingestion of small amounts or if treatment has been delayed. Vomiting should not be induced following ingestion exposures, but the mouth should be rinsed. The person should be kept calm and medical attention should be sought as quickly as possible. For inhalation exposures, removal to fresh air and monitoring for breathing difficulties, respiratory tract irritation, bronchitis, and pneumonitis are recommended. Oxygen should be administered as necessary (PAN, 2005; HSDB, 2005).

CHRONIC EXPOSURE

NONCANCER ENDPOINTS

Little data are available for humans following chronic exposures to alpha-cypermethrin. Chronic exposure to pyrethrins may cause hypersensitivity pneumonitis characterized by chest pain, cough, dyspnea, and

bronchospasm. Because alpha-cypermethrin belongs to this class of chemicals, similar effects may be expected (HSDB, 2005).

Chronic toxicity data are also lacking in animals. No animal data are available for long-term toxicity, reproductive toxicity, teratogenicity, or immunotoxicity (HSDB, 2005; IPCS, 1992). However, chronic toxicity data are available for cypermethrin, including rodent multigenerational reproduction, embryotoxicity, and teratogenicity studies. At doses that produced systemic toxicity, no effects on reproductive parameters or fetal development were observed. Therefore, it is likely that alpha-cypermethrin would also cause no reproductive or developmental effects in rodents because it is a component of cypermethrin. Available data do not indicate that alpha-cypermethrin is mutagenic (IPCS, 1992).

CANCER ENDPOINTS

No data are available on the carcinogenic potential of alpha-cypermethrin (IPCS, 1992).

TOXICOKINETICS

Like other pyrethroid insecticides, orally administered alpha-cypermethrin, is absorbed via the intestinal tract of mammals, and dermally applied doses are absorbed through intact skin. Little or none is absorbed by inhalation exposures (HSDB, 2005). Most pyrethroids are rapidly broken down by liver enzymes and their metabolites are quickly excreted (HSDB, 2005). The metabolism of synthetic pyrethroids in mammals is generally through hydrolysis, oxidation, and conjugation. Metabolism of alpha-cypermethrin occurs by the cleavage of the ester bond. Studies in rats show that the phenoxybenzyl alcohol and cyclpropan carboxylic ac parts of the molecule are conjugated with sulfate and glucuronide, respectively, before being excreted in urine. Esteric hydrolysis and oxidative pathways occur in rats, rabbits, and humans with esteric hydrolysis being the predominant pathway in humans and rabbits (IPCS, 1992). Within 24 hours of an oral dose of 0.25–0.75 mg in humans, 43 percent was excreted in the urine as free of conjugated cis-cyclprpane carboxlic acid (HSDB, 2005; IPCS, 1992). Orally administered alpha-cypermethrin is eliminated in the urine of rats as the sulfate conjugate of 3-(4-hydroxyphenoxy) benzoic acid. In the faces it is eliminated partly as unchanged compound. Alpha-cypermethrin levels in tissues are low except for fatty tissues. The reported half-life for elimination from fat is 2.5 days for the first phase of elimination and 17 to 26 days for the second phase (IPCS, 1992).

ECOLOGICAL EFFECTS

ACUTE EXPOSURE

Toxicity in Non-Targeted Terrestrial Organisms

Alpha-cypermethrin, like other pyrethroids, is very unlikely to harm terrestrial organisms other than its targets (e.g., mosquitoes and other pests). No toxicity data are available for alpha-cypermethrin in birds. However, cypermethrin has a very low toxicity in birds with acute oral LD_{50} values of greater than 2,000 mg/kg body weight. In feed, the reported LC_{50} values are greater than 10,000 mg/kg diet (IPCS, 1992). As with other pyrethroid insecticides, alpha-cypermethrin is extremely toxic to honey bees. The reported 24-hour oral LD_{50} for alpha-cypermethrin emulsifiable concentrate is 0.13 µg/bee and the 24-hour oral LD_{50} for alpha-cypermethrin in acetone was 0.06 µg/bee. The reported dermal LD_{50}s are 0.03 µg/bee for technical alpha-cypermethrin and 0.11 µg/bee for emulsifiable concentrate (IPCS, 1992). The very high toxicity in bees was not observed in the field, likely as a result of the repellent effect of alpha-cypermethrin, which would limit exposure (IPCS, 1992; HSDB, 2005). Mortality was seen in only 15 percent of honey bees exposed to flowers treated with an emulsifiable concentrate formulation within 48 hours. Other studies using oil-enhanced suspension concentrate formulations showed similarly low toxicity. Additionally, a similar pattern of toxicity was seen in leaf-cutting bees. The toxicity of alpha-cypermethrin to earthworms, Carabid beetles, Syrphid

larvae and neuropteran larvae is low while it is relatively high for Linyphiid spiders and Coccinellids (IPCS, 1992).

Toxicity in Non-Targeted Aquatic Systems

Alpha-cypermethrin is very toxic to fish under laboratory conditions, with emulsifiable concentrate formulations being the most toxic (IPCS, 1992); however, these effects are not seen in field studies. Therefore, the hazard to fish from contamination of waterbodies due to overspraying and drift is negligible (IPCS, 1992). Depending on the formulation, the reported 96-hour LC_{50} values range from 0.7 to 350 µg/L (IPCS, 1992). For rainbow trout, the reported 96-hour LC_{50} values range from 2.8 to 350 µg/L (HSDB, 2005; IPCS, 1992). The emulsifiable concentrate formulation is 10 to 70 times more toxic to rainbow trout than the wettable powder or suspension concentrate formulations. However, in field studies, the 14-day LC_{50} for rainbow trout was just 29 g ai/ha for emulsifiable concentrate formulations and greater than 1,000 g ai/ha for suspension concentrate, wettable powder, and micro-encapsulated formulations. For fathead minnows, the reported 96-hour LC_{50} value for technical alpha-cypermethrin was 0.93 µg/L, while the reported 96-hour LC_{50} values for carp range from 0.8 to 11 µg/L depending on the formulation. For fish in the early stages of life, alpha-cypermethrin and cypermethrin toxicity are similar (IPCS, 1992). Alpha-cypermethrin has the potential to accumulate in fish, with a bioconcentration factor of 990 (HSDB, 2005). It has also been shown to be highly toxic to some aquatic invertebrates and aquatic insects (IPCS, 1992).

CHRONIC EXPOSURE

Due to low rate of application and low persistence of alpha-cypermethrin in both terrestrial and aquatic environments, serious adverse effects are not anticipated from chronic exposures (HSDB, 2005). The hazard of alpha-cypermethrin to fish and aquatic invertebrates is in its acute toxicity. There is no evidence of chronic exposure causing cumulative effects (IPCS, 1992).

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PROFILE FOR BENDIOCARB:

CAS REGISTRY NUMBER 22781-23-3

SUMMARY OF INSECTICIDE

CHEMICAL HISTORY

Bendiocarb is a broad spectrum carbamate insecticide first registered in the United States in 1980 for use to control a wide variety of nuisance and disease vector insects, such as mosquitoes, flies, wasps, ants, fleas, cockroaches, silverfish, and ticks. It is also effective against a variety of agricultural insects and to treat seeds against pests (U.S. EPA, 1999a, 1999b; EXTOXNET, 1996). The registration for bendiocarb was voluntarily canceled in 1999 (U.S. EPA, 1999a).

Bendiocarb exhibits its toxic effects through fast-acting, but reversible, cholinesterase inhibition. It has moderate toxicity in mammals (WHO/FAO, 1982), moderate toxicity in birds, and moderate to high toxicity in fish (EXTOXNET, 1996). In humans, symptoms of poisoning are neurological and include headache, blurred vision, nausea, vomiting, giddiness, slurred speech, excessive sweating and salivation, chest tightness, and twitching muscles (WHO/FAO, 1982). Bendiocarb pesticides were formulated as dusts, granules, wettable powders, pellets, and ultra low volume (ULV) sprays (U.S. EPA, 1999a; EXTOXNET, 1996).

DESCRIPTION OF DATA QUALITY AND QUANTITY

Review data for bendiocarb are limited. Relevant resources include

- Bendiocarb: Revised HED Chapter for the Reregistration Eligibility Decision (RED) Document (U.S. EPA, 1999b)
- Data Sheet on Pesticides No. 52: Bendiocarb (WHO/FAO, 1982)
- Pesticide Information Profile for Bendiocarb (EXTOXNET, 1996).

EPA has developed quantitative human health benchmarks (acute and chronic oral RfDs and short-, intermediate-, and long-term dermal and inhalation benchmarks) for bendiocarb.

SUMMARY TABLE

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute, Intermediate, Chronic	Inhalation	0.002	mg/kg/day	Inhalation NOAEL (0.00018 mg/L) for neurological effects with UF of 100 applied	U.S. EPA (1999b)
Acute, Intermediate, Chronic	Oral	0.00125	mg/kg/day	Acute and chronic oral RfDs based on neurological effects; adopt chronic for intermediate duration	U.S. EPA (1999b)
Acute	Dermal	0.5	mg/kg/day	Dermal NOAEL for neurological effects of 50 mg/kg/day with UF of 100 applied	U.S. EPA (1999b)

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Intermediate	Dermal	0.2	mg/kg/day	Dermal LOAEL for neurological effects of 50 mg/kg/day with UF of 300 applied	U.S. EPA (1999b)
Chronic	Dermal	0.00125	mg/kg/day	Oral NOAEL for neurological effects of 0.125 mg/kg/day with UF of 100 applied	U.S. EPA (1999b)

For inhalation exposure, a NOAEL of 0.00018 mg/L (0.2 mg/kg/day)[2] was identified for whole blood cholinesterase inhibition in rats exposed to bendiocarb via inhalation for 6 hours per day, 5 days per week, for 90 days (Coombs et al., 1995). An uncertainty factor of 100 to account for interspecies and intrahuman variation was applied, for an inhalation benchmark of 0.002 mg/kg/day. This value is appropriate for all exposure durations (U.S. EPA, 1999b).

The acute and chronic oral RfDs of 0.00125 mg/kg/day were based on a NOAEL of 0.125 mg/kg for whole blood cholinesterase inhibition (about 25 percent) in rats exposed via gavage five days per week for two weeks (EPA MRID No. 00059269, no additional citation provided), with an uncertainty factor of 100 applied (10 each for interspecies and intrahuman variability). This value was also adopted for intermediate exposure (U.S. EPA, 1999b).

For acute dermal exposures, a NOAEL of 50 mg/kg/day in rats for whole blood cholinesterase inhibition from a single exposure was identified (EPA MRID No. 00122308, no additional citation provided) and an uncertainty factor of 100 was applied (10 each for interspecies and intrahuman variability). For intermediate dermal exposures, a LOAEL of 50 mg/kg/day for whole blood cholinesterase inhibition from repeated dermal exposures was identified (EPA MRID No. 00122308, no additional citation provided) and an uncertainty factor of 300 was applied (10 each for interspecies and intrahuman variability and 3 for the use of a LOAEL). For chronic dermal exposures, the NOAEL that was used to develop the oral RfDs was used with an uncertainty factor of 100 applied (10 each for interspecies and intrahuman variability) (U.S. EPA, 1999b).

INSECTICIDE BACKGROUND

CAS #:	22781-23-3
Synonyms:	2,3-isopropylidenedioxyphenyl methylcarbamate (EXTOXNET, 1996), Ent-27695; OMS 1394; (WHO/FAO, 1982), 1,3-Benzodioxol-4-ol, 2,2-dimethyl-, methylcarbamate , 1,3-Benzodioxole, 2,2-dimethyl-4-(N-methylamino-carboxylato)- , 105201 (U.S. EPA PC Code) , 1924 (CA DPR Chem Code) , 2,2-Dimethyl-1,3-benzodioxol-4-yl methylcarbamate, Carbamic acid, methyl-, 2,3-(dimethylmethylenedioxy)-phenyl ester, Carbamic acid, methyl-, 2,3-(isopropylidenedioxy)phenyl ester (PAN, 2005), bencarbate, 1,3-benzodioxole,2,2,-dimethyl-4(n-methylcarbamato), 2,2-dimethyl-1,3-benzodioxol-4-ol methcarbamate, 2,3-

[2] Conversion between mg/m^3 and mg/kg/day assumes, for Wistar rats, an average body weight of 0.187 kg and inhalation rate of 0.2 m^3/day (U.S. EPA, 1988).

	isopropylidenedioxyphenyl methylcarbamate, methylcarbamic acid 2,3,-(isopropylidenedioxy)phenyl ester (HSDB, 2005)
Chemical Group:	n-methyl carbamate (PAN, 2005)
Registered Trade Names:	Compounds containing bendiocarb: Ficam, Dycarb, Garvox, Multamat, Multimet, Niomil, Rotate, Seedox, Tattoo, Turcam (EXTOXNET, 1996), NC-6897, Ficam D, Ficam plus, Ficam W, Ficam ULV (HSDB, 2005).

USAGE

Bendiocarb is a residual carbamate insecticide that has a variety of indoor and outdoor uses, including the control of mosquitoes, household and ornamental plant pests, and fire ants. It has no registered uses on either food of feed crops (U.S. EPA, 1999b). Most products containing bendiocarb are General Use Pesticides (EXTOXNET, 1996) and are meant for homeowner/residential use. However, some formulations (e.g., wettable powders) are recommended to be used only by pest control operators. Bendiocarb is not a Restricted Use Pesticide (U.S. EPA, 1999b); however, the formulations Turcam and Turcam 2.5 G are classified as *restricted* and may only be used by certified applicators (EXTOXNET, 1996).

Common bendiocarb formulations for both agricultural and public health program uses include wettable powders (800, 500 and 200 g active ingredient/kg [g a.i./kg]), granules for soil and turf treatment (30, 50, and 100 g a.i./kg), dust (10 g a.i./kg), suspension concentrate (500 g a.i./1) for spray or seed treatments, suspension in oil for ULV application (250 g a.i./1), residual sprays, and paint on and granular preparations with bait. The use patterns for bendiocarb in agricultural, horticultural, or forestry applications are reported as follows: soil treatment (300–2,000 g a.i./ha), seed treatment (1–10 g a.i./kg), residual spray (100–1,000 g a.i./ha), and ULV spray (50–500 g a.i./ha). In public health programs, it is reported that the 80 percent wettable powder should be applied only by a professional applicator (WHO/FAO, 1982).

FORMULATIONS AND CONCENTRATIONS

- Common formulations of pesticides containing bendiocarb include technical grade, dusts, granules (for soil and turf treatment: 30, 50, and 100 g a.i./kg), wettable powders (800, 500, and 200 g a.i./kg), dust (10 g a.i./kg), suspension concentrate (for spray or seed treatment: 500 g a.i./L) and ULV sprays (in oil: 250 g, a.i./L) (WHO/FAO, 1982; EXTOXNET, 1996). WHO (1999) indicated that the bendiocarb content in various preparations should be declared and contain the following:
- Technical grade bendiocarb: not less than 940 g/kg
- Wettable Powder: above 250 up to 500 g/kg $\pm$ 5% of the declared content or above 500 g/kg $\pm$ 25 g/kg
- Dustable Powder: shall not differ from the declared content by more than -10% to + 35%.
- ULV Liquid: Above 100 up to 200 g/kg $\pm$ 6% of the declared content (WHO, 1999)

SHELF LIFE

Bendiocarb is reported to be stable below 40°C. Its half-life in aqueous solutions at 25°C is reported as 48 days at pH 5, 81 hours at pH 7, and 45 minutes at pH 9. Bendiocarb degrades slowly at pH 5. Bendiocarb is resistant to oxidation on nonabsorbant surfaces and at low humidity. In sunlight, bendiocarb photo-oxidizes (WHO/FAO, 1982).

DEGRADATION PRODUCTS

In moist soils and water, a major fate process for bendiocarb is hydrolsis. This is particularly true in neutral and alkaline environments. In neutral hydrolysis, the products are 2,3-isopropylidenedioxyphenol, methylamine, and carbon dioxide (HSDB, 2005). At pHs less than 5, bendiocarb slowly degrades into pyrogallol and acetone (WHO/FAO, 1982). The major degradation product of terrestrial field dissipation on turf is NC-7312 (U.S. EPA, 1999b).

ENVIRONMENTAL BEHAVIOR

FATE AND TRANSPORT IN TERRESTRIAL SYSTEMS

Insecticidal carbamates that are applied to plants reach the soil both directly and indirectly. Degradation of carbamates in soil depends on volatility, leaching, soil moisture, absorption, pH, temperature, photodecomposition, microbial degradation, and soil type (IPCS, 1986). With a Koc range of 28 to 200, moderately to very high mobility is expected if bendiocarb is released in soil (HSDB, 2005). The major fate processes are hydrolysis in moist soils and biodegradation, with volatilization being an unimportant fate process for both dry and moist soils due to the low vapor pressure of bendiocarb. In moist soils, bendiocarb may undergo hydrolysis, and hydrolytic degradation depends on pH (HSDB, 2005; U.S. EPA, 1999b). Biodegradation of bendiocarb is expected to be rapid (HSDB, 2005). The half-life of bendiocarb in soil varies from less than 1 week up to 4 weeks, depending on the type of soil and the pH (EXTOXNET, 1996). The estimated hydrolysis half-life of bendiocarb is 46.5 days at pH 5, 2 days at pH 7, and 0.33 days at pH 9 (U.S. EPA, 1999b). Soil photolysis is important in the photodegradation of bendiocarb in soil. In field dissipation studies on turf, bendiocarb and its degradate NC-7312 are not highly mobile, with intermediate half-lives of 20 days (bendiocarb) and 21 days (NC-7312) (U.S. EPA, 1999b). Bendiocarb degrades before leaching through soil, and degradates remain in the upper layers of soil in low concentrations (U.S. EPA, 1999a, 1999b). It is unlikely that bendiocarb will move through soil to groundwater or to surface water through runoff (U.S. EPA, 1999a). Bendiocarb is of low persistence in soil (EXTOXNET, 1996).

FATE AND TRANSPORT IN AQUATIC SYSTEMS

Water is an important factor in the transport of carbamates; however, the hazard posed by carbamates under these conditions is limited due to their rapid decomposition under aqueous conditions (IPCS, 1986). In water, bendiocarb is not expected to adsorb to suspended soils and sediments based on its Koc range (28 to 200). The major fate processes in water are hydrolysis and biodegradation; volatilization is an unimportant fate process due to the low vapor pressure of bendiocarb. Additionally, direct photolysis is not a major degradation pathway in water (U.S. EPA, 1999b) and depends on the turbidity of the water (IPCS, 1986). In alkaline and neutral environments, hydrolysis is expected to be a major fate process. Half-lives have been reported of 48 days at pH 5, 4 days at pH 7, and 45 minutes at pH 9 (HSDB, 2005). Bendiocarb does not accumulate in water (EXTOXNET, 1996), and based on soil studies, biodegradation in water is expected to be rapid (HSDB, 2005). Because bendiocarb degrades rapidly in water, bioconcentration in fish is unlikely (U.S. EPA, 1999a). The estimated bioconcentration factor is 12 (HSDB, 2005).

HUMAN HEALTH EFFECTS

ACUTE EXPOSURE

Effects/Symptoms

Bendiocarb causes toxic effects by the rapid, but reversible, inhibition of cholinesterase in the blood. It is moderately toxic if absorbed through the skin or ingested (EXTOXNET, 1996). Typical signs of acute poisoning are neurological, and include weakness, excessive sweating and salivation, headache, blurred vision,

nausea, vomiting, stomach pain, tightness in the chest, muscular twitching, giddiness, slurred speech, confusion, and muscular incoordination (WHO/FAO, 1982; EXTOXNET, 1996). Death from bendiocarb poisoning can result from paralysis of the respiratory system, severe constriction of the lung openings, or stopped breathing (EXTOXNET, 1996). Little data exist on the human health effects of acute exposure to bendiocarb. In humans, the threshold for mild symptoms and blood cholinesterase inhibition is 0.15–0.20 mg a.i./kg for ingestion. No symptoms were reported following repeated hourly doses of 0.1 mg a.i./kg. Studies in human volunteers have shown that both the onset and recovery from cholinesterase inhibition are very rapid (WHO/FAO, 1982). Case reports of accidental bendiocarb exposures report typical symptoms with reversible cholinesterase inhibition. In one case, cholinesterase was inhibited by 63 percent, and the exposed person recovered in less than 3 hours without any medical treatment. Cholinesterase levels returned to normal within 24 hours. In another case, recovery from symptoms occurred within 2 hours after being decontaminated and treated with atropine, with complete recovery by the next day. Bendiocarb is also a mild irritant to the skin and eyes (EXTOXNET, 1996).

In animals, bendiocarb is acutely toxic via the oral, inhalation, and dermal routes (U.S. EPA, 1999b). The oral LD_{50} values of unformulated bendiocarb in various animal species include 34–156 mg/kg in rats, 35–40 mg/kg in rabbits, and 35 mg/kg in guinea pigs. The reported dermal LD_{50} value in rats is greater than 566 mg/kg (EXTOXNET, 1996; IPCS, 1986; WHO/FAO, 1982) and the reported 4-hour LC_{50} in rats is 0.55 mg/L (EXTOXNET, 1996). For formulated bendiocarb compounds, an LD_{50} of 143–179 mg/kg was reported in rats for an 80 percent a.i. water dispersible powder. A dermal LD_{50} of greater than 1,000 mg/kg was reported for an 80 percent a.i. liquid formulation (WHO/FAO, 1982).

As in humans, acute exposure to bendiocarb in animals causes symptoms typical of cholinesterase inhibition (U.S. EPA, 1999a, 1999b). No acute delayed neurotoxicity was observed in hens. Although bendiocarb causes slight eye irritation in animals, it is not considered a skin or eye irritant or a dermal sensitizer (U.S. EPA, 1999b).

Treatment

Exposure to bendiocarb may be determined through laboratory tests that determine cholinesterase levels in blood; however, the enzyme will only be inhibited for a few hours following exposure. Additionally, bendiocarb metabolites may be identified in urine (WHO/FAO, 1982). Bendiocarb poisoning should be treated in the same way as high-toxicity carbamate poisoning (PAN, 2005). First removing any contaminated clothing and wash affected areas with soap and water. If bendiocarb gets in the eyes, they should be rinsed immediately with isotonic saline or water. Oral exposure to bendiocarb should be treated by rapid gastric lavage with 5 percent sodium bicarbonate if the patient is not already vomiting. Medical attention should be sought. Adults showing signs of bendiocarb toxicity should be treated with 1–2 mg atropine sulfate given intramuscularly or intravenously as needed. Oxygen may be necessary for unconscious patients or those in respiratory distress. Pralidoxime is not effective in treating bendiocarb poisoning (WHO/FAO, 1982).

CHRONIC EXPOSURE

NONCANCER ENDPOINTS

The effects of chronic exposure to bendiocarb in humans have not been well described in the literature, although it is not expected to be toxic at the levels applied to control mosquitoes. When used as a residual mosquito insecticide, few adverse effects were reported by occupationally exposed workers. Those effects that were reported were transient and mild. Additionally, no effects were reported by residents of villages where it was applied (WHO/FAO, 1982).

Subchronic and chronic exposure studies in rats, mice, and dogs have shown that bendiocarb inhibits cholinesterase activity in whole blood, plasma, red blood cells, and the brain (U.S. EPA, 1999a, 1999b; WHO/FAO, 1982). No macroscopic pathology or histological evidence of dermal irritation or treatment-related mortality was observed in a 21-day dermal study in rats. Rats exposed to bendiocarb for 90 days via inhalation showed whole-blood cholinesterase inhibition (U.S. EPA, 1999b). Additionally, bendiocarb does not accumulate in mammalian tissue. There was no evidence of cumulative toxicity in rats or dogs fed bendiocarb for 90 days (WHO/FAO, 1982).

Bendiocarb is not expected to cause reproductive effects in humans. In rats, no effect on fertility and reproduction was seen in rats fed diets containing bendiocarb for three generations. However, very high doses were toxic to dams and pups, as indicated by decreased survival rate and decreased pup weight (EXTOXNET, 1996). No teratogenicity was seen in rats or rabbit fetuses or offspring following pre- and/or postnatal exposures to bendiocarb (U.S. EPA 1999a, 1999b; WHO/FAO, 1982). No evidence of mutagenicity was observed following *in vivo* or *in vitro* exposures to bendiocarb (U.S. EPA, 1999a, 1999b; EXTOXNET, 1996; WHO/FAO, 1982). No irreversible or delayed neurotoxicity has been reported in animals following long-term bendiocarb exposure (WHO/FAO, 1982).

CANCER ENDPOINTS

EPA has classified bendiocarb as a Group E chemical, noncarcingenic to humans (U.S. EPA, 1999b). The classification is based on the lack of increase in tumors in rat and mouse studies and is supported by the lack of mutagenicity in somatic cells (U.S. EPA, 1999b). No human data are available.

TOXICOKINETICS

Bendiocarb can be absorbed through oral, dermal, and inhalation pathways; dermal absorption is especially rapid and is the main route of absorption. Absorption from inhalation, except inhalation of airborne dusts or fine spray mists, is unlikely due to bendiocarb's low vapor pressure (EXTOXNET, 1996; WHO/FAO, 1982). Animal metabolism studies indicate that bendiocarb is rapidly absorbed following oral exposure (U.S. EPA, 1999b). Liver microsome enzymes readily conjugate and metabolize bendiocarb, and it is rapidly excreted. Because of its rapid metabolism and excretion, bendiocarb does not accumulate in mammalian tissues (WHO/FAO, 1982). The majority of an orally administered dose is eliminated in the urine (U.S. EPA, 1999b). In rats fed diets containing up to 10 mg/kg bendiocarb, 89 to 90 percent of the dose was excreted in the urine, 2 to 6 percent was excreted in the feces, and 2 to 6 percent was exhaled. A human subject orally exposed to bendiocarb exhibited a similar excretion pattern (EXTOXNET, 1996). Bendiocarb is excreted mainly as sulfate and beta-glucuronide conjugates of the phenol derivative (WHO/FAO, 1982).

ECOLOGICAL EFFECTS

ACUTE EXPOSURE

When applied at the maximum registered application rate, bendiocarb poses acute risk to nontarget terrestrial organisms, such as mammals and birds (WHO/FAO, 1982; U.S. EPA, 1999a). Single broadcast applications on turf may result in high risk to birds, and multiple applications may result in repeated acute effects (U.S. EPA, 1999a). Oral LD_{50} values range from 3.1 mg a.i./kg body weight in mallard ducks to 137 mg a.i./ kg body weight in domestic hens (WHO/FAO, 1982; U.S. EPA, 1999a). However, bendiocarb does not affect avian reproductive parameters (WHO/FAO, 1982). Additionally, bendiocarb has been found to be highly toxic to bees (WHO/FAO, 1982; EXTOXNET, 1996; U.S. EPA, 1999a), with an oral LD_{50} of 0.0001 mg/bee (EXTOXNET, 1996). Additionally, bendiocarb severely affects earthworms under treated turf (EXTOXNET, 1996).

Bendiocarb poses acute risks to freshwater fish, and estuarine and marine animals (U.S. EPA, 1999a). It is moderately to highly toxic to fish, with LC_{50} values ranging from 0.7 to 1.76 mg a.i./L in various species (U.S. EPA, 1999a; WHO/FAO, 1982). The 96-hour LC_{50} for rainbow trout is 1.55 mg/L (EXTOXNET, 1996). When applied at the maximum registered rate, bendiocarb also poses acute risks to freshwater invertebrates (U.S. EPA, 1999a).

CHRONIC EXPOSURE

Very little data exist for chronic exposure to bendiocarb in nonterrestrial target organisms. In birds, multiple applications of the maximum registered application rate to turf are expected to result in repeated acute effects. The reproductive effects of chronic exposures cannot be assessed due to limited data (U.S. EPA, 1999a).

Little data exist for chronic exposure to bendiocarb in marine or estuarine organisms. When applied at the maximum registered rate, bendiocarb poses chronic risks to freshwater invertebrates. However, it poses no chronic risk to freshwater fish (U.S. EPA, 1999a).

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PROFILE FOR BIFENTHRIN:

CAS REGISTRY NUMBER 82657-04-3

SUMMARY OF INSECTICIDE

CHEMICAL HISTORY

Bifenthrin is a pyrethroid insecticide and acaricide used in agricultural and human health applications (EXTOXNET, 1995; WHO/FAO, 1992). It is primarily available as a wettable powder or an emulsifiable concentrate (EXTOXNET, 1995). Bifenthrin is used to control pests on crops and indoor pests (ATSDR, 2003). For mosquito protection, it is used on bed nets and other materials that are dipped in bifenthrin to protect the user. Bifenthrin is a restricted use pesticide due to its potential toxicity to aquatic organisms, and it may only be purchased and used by certified applicators (ATSDR, 2003; EXTOXNET, 1995).

As a synthetic pyrethroid, bifenthrin exhibits its toxic effects by interfering with the way the nerves and brain normally function (EXTOXNET, 1995). Symptoms of acute exposure may include skin and eye irritation, headache, dizziness, nausea, vomiting, diarrhea, excessive salivation, fatigue, irritability, abnormal sensations of the face and skin, and numbness (PAN, 2005). Inhalation of pyrethrins may cause a localized reaction of the upper and lower respiratory tracts (HSDB, 2005). In mammals, pyrethroids are generally of low toxicity due to their rapid biotransformation (HSDB, 2005). EPA has classified bifenthrin as a Class II chemical or moderately toxic. Bifenthrin is highly toxic to fish and other aquatic organisms (EXTOXNET, 1995).

DESCRIPTION OF DATA QUALITY AND QUANTITY

Several comprehensive reviews on the toxicity of bifenthrin have been prepared or updated in recent years:

- Toxicological Profile for Pyrethrin and Pyrethroids (ATSDR, 2003)
- Pesticide Residues in Food—1992 Evaluation, Part II: Toxicology—Bifenthrin (WHO/FAO, 1992)
- IRIS summary review (U.S. EPA, 2006)
- Pesticide Information Profile for Bifenthrin (EXTOXNET, 1995).

EPA has developed quantitative human health benchmarks (acute and chronic oral RfDs, intermediate-term oral, and short-, intermediate-, and long-term dermal and inhalation benchmarks) for bifenthrin.

SUMMARY TABLE

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute, Intermediate	Inhalation	0.007	mg/kg/day	Oral NOAEL for neurological effects in dogs at 2.21 mg/kg/day with UF of 300 applied	U.S. EPA (2003)
Chronic	Inhalation	0.004	mg/kg/day	Oral NOAEL for neurological effects in dogs at 1.3 mg/kg/day with UF of 300 applied	U.S. EPA (2003)
Acute	Oral	0.033	mg/kg/day	Acute RfD based on neurotoxicity in rats	U.S. EPA (2003)
Intermediate	Oral	0.007	mg/kg/day	Oral NOAEL for neurological effects in dogs at 2.21 mg/kg/day with UF of 300 applied	U.S. EPA (2003)
Chronic	Oral	0.004	mg/kg/day	Chronic RfD based on neurological effects in dogs	U.S. EPA (2003)
Acute, Intermediate, Chronic	Dermal	0.2	mg/kg/day	Dermal NOAEL for neurological effects in rats at 47 mg/kg/day with UF of 300 applied	U.S. EPA (2003)

For oral exposure, an acute RfD of 0.033 mg/kg/day was derived based on a NOAEL of 32.8 mg/kg/day for neurological effects observed in rats exposed to bifenthrin (study citations not provided), with an uncertainty factor of 1,000 applied to account for the lack of a developmental neurotoxicity study and for interspecies and intrahuman variability (U.S. EPA, 2003). An intermediate NOAEL of 2.21 mg/kg/day was identified for tremors in dogs exposed for 90 days and an uncertainty factor of 300 was applied, resulting in a benchmark of 0.007 mg/kg/day (U.S. EPA, 2003). A chronic oral RfD of 0.004 mg/kg/day was derived based on a NOAEL of 1.3 mg/kg/day for tremors in dogs exposed for 1 year, with an uncertainty factor of 300 applied (U.S. EPA, 2003).

For inhalation exposure, an oral NOAEL of 2.21 mg/kg/day was identified for tremors in dogs exposed for 90 days and an uncertainty factor of 300 was applied (U.S. EPA, 2003). This value (0.007 mg/kg/day) is appropriate to use for short- and intermediate-term inhalation exposures. An oral NOAEL of 1.3 mg/kg/day was identified for tremors in dogs exposed for 1 year and an uncertainty factor of 300 was applied (U.S. EPA, 2003). This value (0.004 mg/kg/day) is appropriate to use for long-term inhalation exposures.

For dermal exposure, a NOAEL of 47 mg/kg/day for neurological effects (staggered gait and exaggerated hind limb flexion) was identified in rats dermally exposed to bifenthrin for 21 days. An uncertainty factor of 300 was applied, for a dermal benchmark value of 0.2 mg/kg/day. This value is appropriate for all exposure durations (U.S. EPA, 2003).

INSECTICIDE BACKGROUND

CASRN:	82657-04-3
Synonyms:	(2-methyl[1,1'-biphenyl]-3-yl)methyl 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate, [1alpha, 3alpha(z)]-(+ -)-3-(2-Chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylic acid (2-methyl[1,1'-biphenyl]-3-yl)methyl ester, 2-Methylbiphenyl-3-ylmethyl (z)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoroprop-1- enyl)-2,2-dimethylcyclopropanecarboxylate, [1 alpha, 3 alpha(z)]-(+ -)-(2-Methyl[1,1'-biphenyl]-3-yl)methyl 3-(2-chloro- 3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate (ATSDR, 2003; EXTOXNET, 1995; HSDB, 2005)
Chemical Group:	pyrethroid (PAN, 2005; EXTOXNET, 1995)
Registered Trade Names:	Talstar, Bifenthrine, Biphenate, Brigade, Bifentrina, Biflex, Capture, FMC 54800, FMC 54800 Technical, OMS3024, Torant (with Clofentezine), and Zipak (with Amitraz), Tarstar (HSDB, 2005; EXTOXNET, 1995; ATSDR, 2003; PAN, 2005)

USAGE

Bifenthrin is used as a broad spectrum insecticide and acaricide to combat indoor pests and those on a variety of crops (EXTOXNET, 1995; ATSDR, 2003). It is used to control mosquitoes, beetles, weevils, houseflies, lice, bedbugs, aphids, moths, cockroaches, and locusts. Crops on which bifenthrin is used include alfalfa hay, beans, cantaloupes, cereals, corn, cotton, field and grass seed, hops, melons, oilseed rape, potatoes, peas, raspberries, watermelons, and squash. Bifenthrin belongs to the pyrethroid class of insecticides, which have long been used to control mosquitoes, human lice, beetles, and flies. For mosquito protection, it is used on bed nets and other materials that are dipped into the bifenthrin to protect the user. Bifenthrin for agricultural use is restricted by EPA due to its potential toxicity to aquatic organisms, and it may only be purchased and used by certified applicators (ATSDR, 2003).

FORMULATIONS AND CONCENTRATIONS

Bifenthrin is available in technical grade, emulsifiable concentrate, suspension concentrate, wettable powder, ultra-low volume (ULV) liquid, and granules (HSDB, 2005; EXTOXNET, 1995; WHO, 2001). Technical grade bifenthrin may be mixed with carriers or solvents, resulting in the commercial formulations. The label of products containing bifenthrin must contain the word "warning" (EXTOXNET, 1995). Technical grade bifenthrin must have no less than 920 g/kg bifenthrin. The wettable powder should contain > 25–100 g/kg +/- 10% of the declared content, 100–250 g/kg +/- 6% of the declared content, or > 250–500 g/kg +/- 5% of the declared content (WHO, 2001). Bifenthrin that is used on bed nets for malaria control comes in a suspension concentrate dose of 25 mg a.i./m^2 (WHO, n.d.).

SHELF LIFE

Bifenthrin is photostable and stable to hydrolysis. It volatilizes minimally and is generally stable when stored (EXTOXNET, 1995). Bifenthrin is stable for 2 years at 25–50°C. It is most stable in acidic environments and at pHs from 5 to 9, it is stable for 21 days. Pyrethrins, in general, are stable for a long time in water-based aerosols (HSDB, 2005).

DEGRADATION PRODUCTS

Pyrethroid insecticides are often formulated with synergists that prevent the breakdown of enzymes and thus enhance the activity of the pyrethroid (ATSDR, 2003). The primary metabolic pathway for the breakdown of bifenthrin is ester hydrolysis (HSDB, 2005). The major degradate of bifenthrin metabolism in soil, biota, and water is 4'-hydroxy bifenthrin (Fecko, 1999).

ENVIRONMENTAL BEHAVIOR

FATE AND TRANSPORT IN TERRESTRIAL SYSTEMS

With Koc values ranging from 131,000 to 320,000, the mobility of bifenthrin in soil ranges from low to immobile (HSDB, 2005; EXTOXNET, 1995). Bifenthrin has a low mobility in soils with large amounts of clay, silt, organic matter and in sandy soils without much organic matter (EXTOXNET, 1995). In moist soils, volatilization is a major fate process, although this is lessened by absorption in the soil (HSDB, 2005). Depending on soil type and the amount of air in the soil, the half-life of bifenthrin ranges from 7 days to 8 months (EXTOXNET, 1995). Bifenthrin is expected to biodegrade readily based on its structure and the biodegradation rates of pyrethroids in general (HSDB, 2005). It is not absorbed by plants and dose not translocate in plants (EXTOXNET, 1995).

FATE AND TRANSPORT IN AQUATIC SYSTEMS

Bifenthrin is fairly insoluble in water, so it is unlikely to leach to groundwater and cause significant contamination (EXTOXNET, 1995). Volatilization is a major fate process from surface water; however, because bifenthrin is expected to adsorb to suspended soils and sediments, volatilization is attenuated. Volatilization half-lives of 50 days for a model river and 555 days for a model lake have been reported, but if adsorption is considered, the volatilization half-life of a model pond is 3,100 years. Bifenthrin has a high potential to accumulate in aquatic organisms, with an estimated bioconcentration factor of 190. However, bioconcentration is likely to be lower due to the ability of aquatic organisms to readily metabolize bifenthrin (HSDB, 2005).

HUMAN HEALTH EFFECTS

ACUTE EXPOSURE

Effects/Symptoms

There are limited data on the acute toxicity of bifenthrin in humans. Bifenthrin is classified as having moderate acute toxicity in mammals (EXTOXNET, 1995; WHO/FAO, 1992; PAN, 2005). Incoordination, irritability to sound and touch, tremors, salivation, diarrhea, and vomiting have been caused by high doses. In humans, no skin inflammation or irritation have been observed; however, bifenthrin can cause a reversible tingling sensation (EXTOXNET, 1995).

In animals, the main signs of acute toxicity include clonic convulsions, tremors, and oral discharge (WHO/FAO, 1992). Reported LD_{50} values for bifenthrin include 54–56 mg/kg in female rats, 70 mg/kg in male rats (EXTOXNET, 1995; WHO/FAO, 1992; HSDB, 2005) and 43 mg/kg in mice (WHO/FAO, 1992). Bifenthrin is slightly toxic through dermal contact, with dermal LD_{50}s of over 2,000 mg/kg in rabbits (WHO/FAO, 1992; HSDB, 2005). Neurotoxicity is a key effect of pyrethroids. In mammals, acute exposure to pyrethroids causes tremors, hyperexcitability, salivation, paralysis, and choreoathetosis. However, delayed neurotoxicity has not been observed (HSDB, 2005). Bifenthrin is not a dermal sensitizer in guinea pigs (EXTOXNET, 1995; HSDB, 2005; WHO/FAO, 1992) and did not irritate either abraded or non-abraded skin of rabbits (WHO/FAO, 1992). In rabbits, it is only slightly irritating to the eyes (EXTOXNET, 1995;

WHO/FAO, 1992; HSDB, 2005). Bifenthrin is also a suspected endocrine disruptor (ATSDR, 2003; PAN, 2005).

Treatment

Bifenthrin and its metabolites can be detected in blood and urine during the first few days following exposure (but not later, because these compounds are rapidly broken down in the body) (ATSDR, 2003). Treatment depends on the symptoms of the exposed person. Most casual exposures require only decontamination and supportive care (HSDB, 2005). If a person exhibits signs of typical pyrethroid toxicity following bifenthrin exposure, affected skin areas should be washed promptly with soap and warm water. Medical attention should be sought if irritation or paresthesia occurs. Paresthesia may be prevented or stopped with Vitamin E oil preparations. Corn oil and Vaseline® are less effective and less suitable, and zinc oxide should be avoided (PAN, 2005; HSDB, 2005).

Eye exposures should be treated by rinsing with copious amounts of water or saline. Contact lenses should be removed. Medical attention should be sought if irritation persists (PAN, 2005; HSDB, 2005). Following oral exposures, the person should be kept calm and medical attention should be sought as quickly as possible. Medical personnel will treat severe intoxications with a sedative and anticonvulsant. Ingestion of large amounts of bifenthrin should be treated with gastric lavage, and small ingestions should be treated with activated charcoal and cathartic (PAN, 2005). For sublethal exposures, vomiting may be induced by ipecac and followed by saline cathartic and an activated charcoal slurry, as long as the person is alert and has a gag reflex (HSDB, 2005).

CHRONIC EXPOSURE

Noncancer Endpoints

No data are available for humans following chronic exposures to bifenthrin (EXTOXNET, 1995). Dietary studies in dogs, rats, and mice indicate that oral exposure to bifenthrin causes neurological effects such as tremors (U.S. EPA, 2006; WHO/FAO, 1992) but not cholinesterase inhibition (PAN, 2005). In a 1-year feeding study in dogs and a lifetime feeding study in mice, intermittent tremors were observed (U.S. EPA, 2006; WHO/FAO, 1992). In subchronic duration exposure studies in dogs and rats, tremors were also seen at higher exposure levels (U.S. EPA, 2006; WHO/FAO, 1992).

Bifenthrin has the potential to be reproductive toxin (PAN, 2005). Reproductive toxicity has been observed in rats and rabbits at doses lower than those that cause tremors (EXTOXNET, 1995). Teratogenicity was not observed in a 2-generation rat study (EXTOXNET, 1995) or a rabbit teratogenicity study (WHO/FAO, 1992; HSDB, 2005).

Additional effects observed in chronic exposure animal studies include increased body weight and organ-to-body ratios (U.S. EPA, 2006). The mutagenicity data are inconclusive for bifenthrin (EXTOXNET, 1995), but it is unlikely to pose a genetic hazard (WHO/FAO, 1992).

Cancer Endpoints

EPA has classified bifenthrin as Class C, possible human carcinogen (EXTOXNET, 1995; PAN 2005). A 2-year, high dose dietary exposure study in rats reported no evidence of cancer. In mice, however, a significant dose-related increase in urinary bladder tumors was observed in male mice. An increased incidence of lung tumors was observed in female mice (U.S. EPA, 2003; EXTOXNET, 1995).

TOXICOKINETICS

Bifenthrin is readily absorbed through intact skin (EXTOXNET, 1995; HSDB, 2005) and the gastrointestinal tract (WHO/FAO, 1992). It breaks down in the same way as other pyrethroids (EXTOXNET, 1995). Hydrolysis and hydroxylation are the primary steps in the transformation of bifenthrin. In poultry, bifenthrin

metabolism begins with hydroxylation of the 2-methyl carbon of the cyclopropane ring, followed by fatty acid conjugation (WHO/FAO, 1992). Oral administration of radioactive pyrethroids have been shown to distribute to every tissue examined (HSDB, 2005). Bifenthrin can accumulate in fatty tissues such as skin and ovaries (EXTOXNET, 1995). Bifenthrin metabolism and excretion are rapid. In rats given 4–5 mg/kg bifenthrin, 70 percent of the dose was excreted in urine within 7 days, and 20 percent was excreted in feces (EXTOXNET, 1995). However, another study in rats showed that following oral administration of bifenthrin, 70 to 80 percent was eliminated in the feces within 48 hours while only 5 to 10 percent was eliminated in the urine. Biliary excretion raged from 20 to 30 percent (WHO/FAO, 1992).

ECOLOGICAL EFFECTS

ACUTE EXPOSURE

Toxicity in Non-Targeted Terrestrial Organisms

Bifenthrin, like other pyrethroids, is unlikely to harm terrestrial organisms other than its targets, such as mosquitoes and other pests, due to its low persistence in the environment (HSDB, 2005). Bifenthrin has a moderate toxicity in birds (EXTOXNET, 1995). The 8-day dietary LC_{50} values range from 1,280 ppm in mallard ducks to 4,450 ppm in bobwhite quail. Oral LD_{50} values range from 1,800 mg/kg in bobwhite quail to 2,150 mg/kg in mallard ducks. Additionally, concerns about bioaccumulation in birds have been reported. As with other pyrethroid insecticides, bifenthrin is extremely toxic to honey bees (EXTOXNET, 1995; HSDB, 2005).

Toxicity in Non-Targeted Aquatic Systems

Bifenthrin is also known to be toxic to a wide variety of aquatic organisms, including fish, crustaceans, aquatic insects, mollusks, nematodes, flatworms, phytoplankton, and zooplankton (PAN, 2005). Bifenthrin is very toxic to fish (EXTOXNET, 1995); however, because it is not very water soluble and has a high affinity for soil, the risk to aquatic systems is not expected to be high (EXTOXNET, 1995). The high toxicity in fish is illustrated by the low exposures that cause lethality. The reported 96-hour LC_{50} is 0.00015 mg/L in rainbow trout and 0.00035 mg/L in bluegill sunfish (EXTOXNET, 1995; HSDB, 2005). Average LC_{50} values are 17.5 µg/L in sheepshead minnow and 0.36 µg/L in gizzard shad (PAN, 2005). In Daphnia, the reported 48-hour LC_{50} is 0.0016 mg/L (HSDB, 2005). The risk of bioaccumulation of the bifenthrin formulation Talstar®100EC in aquatic organisms is reported to be very high (ASTRACHEM, n.d.). The whole-body bioconcentration factor values for fathead minnow in water T a concentration of 0.0037 µg/L were 21,000 (over 127 days) and 28,000 (over 254 days) (CalDFG, 2000).

CHRONIC EXPOSURE

Toxicity in Non-Targeted Terrestrial Organisms

No data were located on the chronic toxicity to nontarget terrestrial organisms.

Toxicity in Non-Targeted Aquatic Systems

Chronic exposure of fathead minnow to a 95.7 percent bifenthrin formulation for 246 days resulted in a reported LOEC of 0.41 µg/L, NOEC of 0.30 µg/L, and MATC of 0.351 µg/L. Chronic exposure of fathead minnow to a 96.2 percent bifenthrin formulation for 346 days resulted in a reported LOEC of 0.090 µg/L, NOEC of 0.050 µg/L, and MATC of 0.067 µg/L (CalDFG, 2000).

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PROFILE FOR CHLORPYRIFOS

CAS REGISTRY NUMBER 2921-88-2

CHEMICAL SUMMARY

Chlorpyrifos (phosphorothioic acid, O,O-diethylO-[3,5,6-trichloro-2-pyridinyl] ester) is an organophosphate insecticide/acaricide/miticide used on a wide variety of terrestrial and greenhouse food and feed crops, terrestrial and greenhouse non-food crops, and non-agricultural indoor and outdoor sites (e.g., golf courses). Public health uses include aerial and ground-based treatments to control mosquitoes. It is also used in ant and roach bait products and fire ant treatments. It was first registered in 1965 (EPA 2016).

Chlorpyrifos toxicity in animals is based upon binding to and inhibition of the enzyme acetylcholinesterase (AChE). Inhibition of AChE leads to accumulation of acetylcholine, and interferes with proper neurotransmission in cholinergic synapses and neuromuscular junctions, which in turn can lead to sublethal effects and mortality. The effects of chlorpyrifos have been studied extensively in human, mammalian (e.g., rats, mice, rabbits, dogs) (EPA 2011, 2014), and nonmammalian species (e.g., fish and aquatic/terrestrial invertebrates) (EPA 2016). AChE inhibition is generally used as the most sensitive dose-response endpoint, and the potential for neurodevelopmental effects has been assessed in humans. Larger doses can result in death, respiratory distress, cardiovascular effects, and musculosketal effects; all largely related to AChE inhibition. Chlorpyrifos is judged by EPA as not likely to be carcinogenic in humans.

HUMAN HEALTH EFFECTS

DATA QUALITY AND QUANTITY

Chlorpyrifos has been extensively studied and reviewed in terms of human toxicity. It is currently undergoing pesticide registration review by EPA. Key recent regulatory reports include the following:

- EPA 2011. Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration Review
- EPA 2014. Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review
- EPA 2000. Registration Eligibility Science Chapter for Chlorpyrifos
- WHO 2004. Chlorpyrifos in Drinking Water
- WHO 2015: WHO Specifications and Evaluations for Public Health Pesticides: Chlorpyrifos

Additionally, the following older ATSDR report was reviewed:

- ATSDR 1997. Toxicological Profile for Chlorpyrifos

Chlorpyrifos is not currently listed in EPA's Human Health Benchmarks for Pesticides database (https://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home:2290026002930314), presumably because it is currently under review. EPA is proposing to revoke existing food tolerances for chlorpyrifos (EPA 2015).

TOXICITY

An Agency for Toxic Substances and Disease Registry (ATSDR) Minimum Risk Level (MRL) of 0.003 mg/kg/d has been derived for both acute (14 d or less) and intermediate (15-364 d) oral exposure to chlorpyrifos (ATSDR 1997). These MRLs are based upon a study in which 16 human adult male volunteers (4 per dose group) were administered chlorpyrifos in doses of 0, 0.014, 0.03, or 0.1 mg/kg once daily in a tablet with breakfast for up to 28 d. The highest dose that can be unequivocally stated to be a no-observed adverse effect level (NOAEL) in this study is the 0.03 mg/kg/d dosage. The calculated MRL of 0.003 mg/kg/d (with an uncertainty factor or UF of 10 applied) is considered "adequate to afford protection from all adverse health effects that have been associated experimentally as well as clinically with acute- and

intermediate-duration exposure to chlorpyrifos" (ATSDR 1997). This value has been adopted by EPA in its Regional Screening Levels (https://www.epa.gov/risk/regional-screening-levels-rsls-users-guide-may-2016) as a Reference Dose (RfD).

For chronic oral exposure, ATSDR derived an MRL of 0.001 mg/kg/d. This was derived from a study in which Sherman rats were fed chlorpyrifos at levels corresponding to 0, 0.01, 0.03, 0.1, 1, or 3 mg/kg/d for 2 years, beginning at 7 weeks of age. Doses of 0.1 mg/kg/d and below had no effect on red blood cell (RBC) cholinesterase. Based on the NOAEL of 0.1 mg/kg/d for cholinesterase inhibition, an MRL of 0.001 mg/kg/d was calculated, using UFs of 10 for interspecies extrapolation and 10 for intraspecies variability in susceptibility.

The World Health Organization (WHO) has established Acceptable Daily Intakes (ADIs) for chlorpyrifos. The toxicology of chlorpyrifos was first evaluated in 1972, when an ADI of 0 to 0.0015 mg/kg/d was established on the basis of a NOAEL of 0.014 mg/kg/d in a 1-month study in humans. Further biochemical and toxicological information was considered in 1977, when the ADI was changed to 0 to 0.001 mg/kg/d. Additional reports on the toxicology of chlorpyrifos were reviewed in 1982, which increased the ADI to 0 to 0.01 mg/kg/d on the basis of a NOAEL of 0.1 mg/kg/d in humans exposed to chlorpyrifos for 9 d, with a 10-fold safety factor. The latest (WHO 2004, 2015) ADI is 0 to 0.01 mg/kg/d, based upon studies of multiple species and including a 100 (for animals) to 10 (for humans) fold safety factor. An acute reference dose (RfD) was established as 0.1 mg/kg/d from human volunteers who received a single oral dose of chlorpyrifos. This was based upon a NOAEL of 1 mg/kg for inhibition of erythrocyte AChE activity, and incorporating a safety factor of 10.

EPA recently conducted a chlorpyifos risk assessment as part of registration review (EPA 2014). EPA applied its Data-Derived Extrapolation Factor (DDEF) guidance in its use of a physiologically-based pharmacokinetic-pharmacodynamic (PBPK-PD) model. The PBPK-PD model estimated human RBC AChE inhibition from exposures via oral, dermal, and inhalation routes. The PBPK-PD model was used to estimate exposure levels resulting in 10% RBC AChE inhibition following acute (1 d, 24 hours) and steady state (21-d) exposures for a variety of exposure scenarios for chlorpyrifos and/or chlorpyrifos oxon. Separate points of departure (PoDs) were calculated for dietary (food, drinking water), residential, and occupational exposures by varying inputs; and applied to human data from epidemiological cohorts. Table 4.8.4, reproduced at the end of this section as Figure 1, is a summary of the PoDs estimated.

The main differences between the older ATSDR and WHO values, as compared to the more recent EPA values, are attributable to the following:

1. Differences in data employed. The EPA (2014) assessment used recent epidemiological studies as a basis, while the older ATSDR and WHO values rely on early human experimental data.
2. Differences in how UFs or safety factors were derived, and differences in how these were applied. The EPA 2014 risk assessment used a PBPK-PD model to refine these, under particular receptor and exposure scenarios.

However, note that in most cases the benchmark values from these different studies are within an order-of-magnitude.

HUMAN TOXICITY BENCHMARK SUMMARY

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute	Oral	0.003	mg/kg/d	Based upon NOAEL (depressed AChE seen in higher doses), human study, includes 10x UF	ATSDR 1997

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Subchronic	Oral	0.003	mg/kg/d	Based upon NOAEL (depressed AChE seen in higher doses), human study, includes 10x UF	ATSDR 1997
Chronic	Oral	0.001	mg/kg/d	Based upon NOAEL (depressed AChE seen in higher doses), rat study, includes 10x UF	ATSDR 1997
Acute	Oral (food)	0.0047	mg/kg/d	Oral acute point of departure (PoD) of 467 µg/kg/d from PBPK-PD model for adult female subgroup (Table 4.8.4). Acute PAD calculated by EPA applying a UF of 100 (10x intraspecies, 10x FQPA safety factor).	EPA 2014
Intermediate	Oral (food)	0.00078	mg/kg/d	21-d exposure PoD of 78 µg/kg/d from PBPK-PD model for adult female subgroup (Table 4.8.4). Intermediate PAD calculated by EPA applying a UF of 100 (10x intraspecies, 10x FQPA safety factor).	EPA 2014
Acute	Oral	0.1	mg/kg/d	Based upon NOAEL of 1 mg/kg/d (depressed AChE seen in higher doses), human study, safety factor of 10	WHO 2015
Chronic	Oral	0.01	mg/kg/d	Based upon NOAEL of 0.1 mg/kg/d (depressed AChE seen in higher doses), human study, safety factor of 10.	WHO 2004, 2015

Abbreviations: AChE= acetylcholinesterase, FQPA= Food Quality Protection Act, NOAEL= no observed adverse effect level, PAD= population adjusted dose, PBPK-PD = physiologically based pharmacokinetic/pharcodynamic model, POD= point of departure, UF=uncertainty factor

ECOLOGICAL EFFECTS

DATA QUALITY AND QUANTITY

EPA is currently conducting Biological Evaluations (BEs) for assessing risks to threatened and endangered species from selected pesticides (https://www.epa.gov/endangered-species/biological-evaluation-chapters-chlorpyrifos-esa-assessment#exec-summary). These BEs include many types of terrestrial, aquatic (both freshwater and marine), and avian animal species; as well as plants. In 2009, EPA (2009) conducted a BE for chlorpyrifos and a number of aquatic, avian, and terrestrial species found in California and their designated critical habitat, if applicable. EPA made "May Affect" and "Likely to Adversely Affect" determinations for all of the species and critical habitats assessed. However, benchmarks from this study were not published.

The majority of studies and information are available for aquatic toxicity, as described below.

ENVIRONMENTAL BEHAVIOR

Chlorpyrifos' use as an insecticide will result in its direct release to the environment. A vapor pressure of 2.02E-05 mm Hg at 25 deg C implies that chlorpyrifos will exist in both the vapor and particulate phases in the atmosphere. Vapor-phase chlorpyrifos will be degraded in the atmosphere by reaction with hydroxyl radicals, with a half-life of 5 hours. Particulate-phase chlorpyrifos will be removed from the atmosphere by wet or dry deposition (NLM 2016).

The primary environmental degradation products are organochlorine compounds and carbon dioxide. Chlorpyrifos absorbs light at wavelengths greater than 295 nm, and photolysis has been observed in air. The summer photolysis half-life is estimated as 4.2 d with the winter photolysis half-life estimated as 9.7 d. If released to soil, chlorpyrifos is expected to have low to no mobility based upon a measured K_{oc} range of 995 to 31,000. Volatilization from moist soil surfaces may be an important fate process based upon a Henry's Law constant of 3.55E-05 atm-m^3/mole. The volatilization half-life of chlorpyrifos was 0.64% volatilization after 3.2 d. In several tests lasting 7-11 d, chlorpyrifos applied to turf lost a mean amount of 8.25% to volatilization. Photodegradation and biodegradation in soil have been observed. Half-lives range from 33-56 d for soil incorporated applications and 7-15 d for surface applications (NLM 2016).

If released into water, chlorpyrifos is expected to adsorb to suspended solids and sediment. Volatilization from water surfaces is expected to be an important fate process based upon the Henry's Law constant. Estimated volatilization half-lives for a model river and lake were 2.2 and 21.5 d, respectively. Volatilization from water surfaces is expected to be attenuated by adsorption to suspended solids and sediment. The estimated volatilization half-life from a model pond was 2 years, if adsorption is considered. Hydrolysis half-lives at 25 deg C in aqueous buffers at pH 5, pH 7 and pH 9 were 72, 72 and 16 d respectively. Biodegradation is expected to be an important fate process. Chlorpyrifos degraded about 40% faster in active (natural) water as compared to the same water which had been sterilized with formalin. The reported half-life in active water was 24.5 d (NLM 2016).

Measured bioconcentration factor (BCF) values are availalble for a variety of aquatic organisms. A measured log BCF value for chlorpyrifos of 2.67 (BCF of 468) was determined from a 35-d flowing-water study using mosquito fish, and a log BCF value of 2.50 was determined from a static ecosystem study using mosquito fish. In a review of the environmental fate of chlorpyrifos, BCF values of 100-4,667 were reported in a variety of fish under field conditions. BCF values of 58-1,000 were reported in a variety of fish using flow-through aquariums. A BCF of 2727 was measured in Bluegill (Lepomis macrochirus). A BCF range of 49-2880 was measured in carp.

TOXICITY

Chlorpyrifos has been extensively studied and reviewed in terms of aquatic toxicity under the Clean Water Act. It is currently undergoing pesticide registration review by EPA. The following values are from the EPA

Office of Pesticide Programs database (at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/aquatic-life-benchmarks-pesticide-registration).

ECOLOGICAL TOXICITY BENCHMARK SUMMARY

Duration	Species	Value	Units	Endpoint	Reference
Acute	Fish	0.9	ug/L	Toxicity value x LOC. For acute fish, toxicity value is generally the lowest 96-hour LC50 in a standardized test (usually with rainbow trout, fathead minnow, or bluegill), and the LOC is 0.5.	a
Chronic	Fish	0.57	ug/L	Toxicity value x LOC. For chronic fish, toxicity value is usually the lowest NOEAC from a life-cycle or early life stage test (usually with rainbow trout or fathead minnow), and the LOC is 1.	a
Acute	Invertebrates	0.05	ug/L	Toxicity value x LOC. For acute invertebrate, toxicity value is usually the lowest 48- or 96-hour EC50 or LC50 in a standardized test (usually with midge, scud, or daphnids), and the LOC is 0.5.	a
Chronic	Invertebrate	0.04	ug/L	Toxicity value x LOC. For chronic invertebrates, toxicity value is usually the lowest NOAEC from a life-cycle test with invertebrates (usually with midge, scud, or daphnids), and the LOC is 1.	a
Acute	Nonvascular Plants	140	ug/L	Toxicity value x LOC. For acute nonvascular plants, toxicity value is usually a short-term (less than 10 d) EC50 (usually with green algae or diatoms), and the LOC is 1.	a
Criterion Maximum Concentration (acute)	--	0.083	ug/L	One toxicity value integrates results from different taxonomic groups. Based on lower 5th percentile of species-sensitivity distribution. Individual toxicity values are averaged within genera to form distribution of genus means.	b

Duration	Species	Value	Units	Endpoint	Reference
Criterion Continuous Concentration (chronic)	--	0.041	ug/L	One toxicity value integrates results from different taxonomic groups. Based on lower 5th percentile of species-sensitivity distribution. Individual toxicity values are averaged within genera to form distribution of genus means.	b

Notes: Values from https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/aquatic-life-benchmarks-pesticide-registration

Abbreviations: EC_{50}= 50% effect concentration, LC_{50}= 50% lethal concentration, LOC=level of concern, NOAEC=no observed adverse effect concentration

a: EPA Office of Pesticide Programs Aquatic Life Benchmarks

b: EPA Office of Water Aquatic Life Criteria

The ecological data annex (D-4) contains further information on ecological toxicity values.

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FIGURE 1: TABLE 4.8.4 FROM EPA (2014).

Table 4.8.4. Chlorpyrifos PBPK Modeled Doses (PoDs) Corresponding to 10% RBC AChE Inhibition

RA Type	Exposure Pathway (all chlorpyrifos unless noted)	Infants (< 1 yr old)		Young Children (1 - 2 years old)		Children (Residential:6-11 years old; Dietary:6-12 years old)		Youths (Residential:11-16 years old; Dietary:13-19 years old)		Females (13 – 49 years old)	
		Acute	Steady State (21 day)	Acute	Steady State (21 day)	Acute	Steady State (21 day)	Acute	Steady State (21 day)	Acute	Steady State (21 day)
Dietary	Drinking Water (oxon conc, ppb)	1,183	217	3,004	548	7,700	1,358	4,988	878	5,285	932
	Food (ug/kg/day)	600	103	581	99	530	90	475	80	467	78
Residential (Golfers)	Dermal (ug/kg/day)						25,750		13,950		11,890
Residential (Mosquitocide Application)	Dermal (ug/kg/day)				134,250						23,600
	Oral (ug/kg/day)				101						
	Inhalation (concn. in air mg/m3)				2.37						6.15
Occupational	Dermal (ug/kg/day)										3,630
	Inhalation (ug/kg/day)										138

*PoDs and exposure and risk estimates for females 13-49 yrs covers all youths >13 yrs

PROFILE FOR CYFLUTHRIN:

CAS REGISTRY NUMBER 68359-37-5

SUMMARY

CHEMICAL HISTORY

Cyfluthrin is a synthetic pyrethroid insecticide first registered by EPA in 1987. It is used in agricultural and human health applications against a wide variety of pests. It is similar to the natural insecticide pyrethrum, which comes from chrysanthemums; however, it is more effective and longer lasting (ATSDR, 2003). Cyfluthrin has both contact and stomach poison action (EXTOXNET, 1998) and it interferes with nervous system transmissions through inhibition of the sodium channel system (WHO, 2004). It is available as the technical product, emulsifiable concentrate, wettable powder, aerosol, granule, liquid, oil-in-water emulsion, dust, concentrate, and ultra-light-volume oil spray (EXTOXNET, 1998; IPCS, 1997). For mosquito control, it is used in bed nets and other materials that are treated with cyfluthrin to protect the user (WHO, 1998). Cyfluthrin can be found in both restricted use pesticides and general use pesticides (EXTOXNET, 1998). When used, it is applied by spraying, dusting, fogging, or impregnation (WHO, 2004; IPCS, 1997). It is considered moderately toxic to mammals (EXTOXNET, 1998). Typical symptoms of acute human exposure are skin and eye irritation. Dermal irritation may include itching, burning, or stinging, which may lead to a numbness that lasts up to 24 hours. Skin irritation may occur immediately following exposure or be delayed for 1 to 2 hours (EXTOXNET, 1998). In animals, very high doses have been shown to cause nervous system effects, including irritability, excessive salivation, uncoordinated gait, tremors, convulsions, and death (EXTOXNET, 1998; ATSDR, 2003).

DESCRIPTION OF DATA QUALITY AND QUANTITY

EPA has developed a quantitative human health benchmark for cyfluthrin (EPA's chronic oral RfD). Several reviews on the toxicity of cyfluthrin have been prepared or updated in recent years and recommended resources include the following:

- Toxicological Profile for Pyrethrin and Pyrethroids (ATSDR, 2003)
- IRIS summary review (U.S. EPA, 2005b)
- Pesticide Information Profiles: Cyfluthrin (EXTOXNET, 1998)
- Toxicological Evaluation of Certain Veterinary Drug Residues in Food. WHO Food Additives Series 39: Cyfluthrin (IPCS, 1997)
- Specifications and Evaluations for Public Health Pesticides: Cyfluthrin (WHO, 2004).

SUMMARY TABLE

	Route	Benchmark Value	Units	Endpoint	Reference
Acute	Inhalation	0.0007	mg/kg/day	Inhalation NOAEL in rats with UF of 100 applied	U.S. EPA (2005a)
Intermediate, Chronic	Inhalation	0.0002	mg/kg/day	Inhalation NOAEL in rats with UF of 100 applied	U.S. EPA (2005a)

Acute	Oral	0.02	mg/kg/day	Acute RfD based on mammalian neurotoxicity	U.S. EPA (2005a)
Intermediate	Oral	0.024	mg/kg/day	Adopt chronic RfD for intermediate duration	
Chronic	Oral	0.024	mg/kg/day	Chronic RfD based on neurological effects in dogs	U.S. EPA (2005a)
Acute, Intermediate, Chronic	Dermal	3	mg/kg/day	Dermal NOAEL in rabbits with UF of 100 applied	

For inhalation exposure, a NOAEL of 0.00026 mg/L (0.07 mg/kg/day) was identified for body weight effects in rats exposed to beta-cyfluthrin via inhalation for 28 days. A NOAEL of 0.00009 mg/L (0.02 mg/kg/day) was identified for neurological and body weight effects in rats exposed to cyfluthrin via inhalation for 13 weeks. An uncertainty factor of 100 to account for inter- and intraspecies variation was applied, for a short-term inhalation benchmark of 0.0007 mg/kg/day and an intermediate- and long-term inhalation benchmark of 0.0002 mg/kg/day.

For oral exposure, an acute oral RfD of 0.02 mg/kg/day was derived based on a NOAEL of 2 mg/kg/day for acute mammalian neurotoxicity following exposure to beta-cyfluthrin. An uncertainty factor of 100 was applied for inter- and intraspecies variability (U.S. EPA, 2005a). A chronic oral RfD of 0.024 mg/kg/day was derived based on a NOAEL of 2.4 mg/kg/day for neurological effects in dogs exposed to cyfluthrin for 53 weeks. An uncertainty factor of 100 was applied for inter- and intraspecies variability (U.S. EPA, 2005a). An intermediate oral RfD of 0.024 mg/kg/day was derived based on a NOAEL of 2.4 mg/kg/day for neurological effects in dogs exposed to beta-cyfluthrin for 90 days. An uncertainty factor of 100 was applied for inter- and intraspecies variability (U.S. EPA, 2005a).

For dermal exposure, a NOAEL of 250 mg/kg/day (85 percent purity) was identified in rabbits dermally exposed to cyfluthrin 5 times a week for 6 hr/day for 3 weeks (IPCS, 1997). An uncertainty factor of 100 to account for inter- and intraspecies variation was applied, for a dermal benchmark value of 3 mg/kg/day. This value is appropriate for all exposure durations.

INSECTICIDE BACKGROUND

CASRN:	68359-37-5
Synonyms:	Cyano(4-fluoro-3-phenoxyphenyl) methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate; BAY-FCR 1272; (R,S)-alpha-Cyano-4-fluoro-3-phenoxybenzyl-(1R,S)-cis,trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate; 3-(2,2-Dichloroethenyl)-2,2-diethylcyclopropanecarboxylic acid cyano(4-fluoro- 3-phenoxyphenyl)methyl ester; Cyfluthrine; FCR 1272; (RS)-alpha-Cyano-4-fluoro-3-phenoxybenzyl (1RS, 3RS: 1RS, 3SR)-3-(2,2- dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (ATSDR, 2003; HSDB 2005)
Chemical Group:	pyrethroid (ATSDR, 2003)

Registered Trade Names: Attotox, Baythroid, Baygon aerosol, Baythroid H, Cyfoxlate, Contur, Laser, Responsar, Solfac, Tempo, Tempo H (ATSDR, 2003; EXTOXNET, 1998)

USAGE

Cyfluthrin is effective in combating a broad spectrum of insect pests in agricultural, public health, and structural applications (WHO, 2004; EXTOXNET, 1998). The main agricultural use of cyfluthrin is against chewing and sucking insects on crops (EXTOXNET, 1998; HSDB, 2005; ATSDR 2003). In public health applications, it is used to control mosquitoes, houseflies, and cockroaches (HSDB, 2005). It is primarily a contact insecticide and is applied by residual spraying, fogging, or impregnation (WHO, 2004).

FORMULATIONS AND CONCENTRATIONS

Cyfluthrin is available in technical grade, emulsifiable concentrate, wettable powder, aerosol, granules, liquid, oil-in-water emulsion, and ultra-light-volume oil sprays (EXTOXNET, 1998; HSDB 2005). Technical grade cyfluthrin may be mixed with carriers or solvents resulting in the commercial formulations. These commercial formulations may also include ingredients that may potentiate the toxicity compared to technical grade cyfluthrin (EXTOXNET, 2005). WHO indicates that the content of cypermethrin in the formulated products must be declared and shall not exceed the listed standards. Technical grade cyfluthrin must have no less than 920 g/kg cyfluthrin and should contain the four diastereoisomers as follows:

- Diastereoisomer I, (R)-alpha-cyano-4-fluoro-3-phenoxybenzyl-(1R)-cis -3-(2,2-dichlorovinyl)-2,2- dimethylcyclopropanecarboxylate + (S)-alpha, (1S)-cis: 23–27 percent
- Diastereoisomer II, (S)-alpha-cyano-4-fluoro-3-phenoxybenzyl-(1R)-cis -3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate + (R)-alpha, (1S)-cis: 17–21 percent
- Diastereoisomer III, (R)-alpha-cyano-4-fluoro-3-phenoxybenzyl-(1R)-trans -3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate + (S)-alpha, (1S)-trans: 32–36 percent
- Diastereoisomer IV, (S)-alpha-cyano-4-fluoro-3-phenoxybenzyl-(1R)- trans -3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate + (R)-alpha, (1S)-trans: 21–25 percent.

The wettable powder should contain 100 g/kg cyfluthrin +/- 10 percent of the declared content. The oil-in-water emulsion shall contain 50 g/kg or g/L cyfluthrin +/- 10 percent of the declared content at 20 +/- 2 ^{o}C (WHO, 2004, ATSDR, 2003). For malaria control, a 10 percent wettable powder formulation has been found to be safe and effective for indoor residual spraying against malaria vectors at target doses of 15 to 50 mg/m^2, while a 5 percent oil in water emulsion is effective and safe for use in impregnation of bed nets at a dose of 50 mg/m^2 (WHO, 1998).

SHELF LIFE

Cyfluthrin in water-based aerosols is stable for a long time. It is thermally stable at room temperature. Topical cyfluthrin preparations made with piperonyl butoxide should be stored at temperatures below 40 ^{o}C (and optimally at 15 to 30 ^{o}C) and in tightly closed containers (HSDB, 2005). Australian researchers reported that cyfluthrin is stable and does not break down for up to 52 weeks when used on stored wheat (EXTOXNET, 1998).

DEGRADATION PRODUCTS

Pyrethroid insecticides are often formulated with synergists that act to prevent the breakdown of enzymes and thus enhance the activity of the pyrethroid (ATSDR, 2003). Cyfluthrin's breakdown products include 4-

fluoro-3-phenoxybenzoic acid (PAN, 2005). In soil, the primary breakdown products include carbon dioxide and 4-fluoro-3-phenyl-benzaldehyde (a compound of considerably lower toxicity than the parent compound) (EXTOXNET, 1998).

ENVIRONMENTAL BEHAVIOR

FATE AND TRANSPORT IN TERRESTRIAL SYSTEMS

The use of cyfluthrin as an insecticide may result in its release into the environment via a variety of waste streams (HSDB, 2005). Once in the environment, cyfluthrin is expected to be highly immobile in the soil based on its Koc value (HSDB, 2005; EXTOXNET, 1998). Because it is immobile in soil, cyfluthrin does not easily leach into groundwater (EXTOXNET, 1998).

Cyfluthrin is one of the more persistent pyrethroids and as a result, it is used more often in agricultural applications (ATSDR, 2003). It can be broken down by sunlight, and in surface soils, the reported half-life ranges from 48 to 72 hours. Reported half-lives in German loam and sandy loam soils are 51 to 63 days. Persistence under anaerobic conditions is similar. The persistence of cyfluthrin in soil is not significantly affected by soil moisture content (EXTOXNET, 1998; ATSDR, 2003).

The major fate processes for cyfluthrin in soil are biodegradation and photolysis. Under anaerobic conditions, more than 90 percent biodegradation was reported during an incubation period of 140 days. Anaerobic biodegradation of cyfluthrin initially produces 3-(2,2-dichlorovinyl)2,2-dimethylcyclopropancarboxcylic acid and 4-fluoro-3-phenoxybenzoic acid. Photodegradation was observed when cotton fabric was irradiated for 96 hours in simulated natural sunlight, resulting in almost 75 percent photo-degradation (HSDB, 2005). Volatilization is not expected to be a major fate process from either moist or dry soils (HSDB, 2005).

FATE AND TRANSPORT IN AQUATIC SYSTEMS

Cyfluthrin binds tightly to soil, is practically insoluble in water, and is less dense than water, allowing it to float on the surface film of natural water (EXTOXNET, 1998; HSDB, 2005). It is stable in water under acidic conditions but hydrolyzes rapidly under basic conditions (EXTOXNET, 1998). On surface waters, cyfluthrin breaks down by photolysis and is not expected to volatilize (EXTOXNET, 1998; HSDB, 2005). In aqueous solutions, an experimental half-life of 16 hours was identified when irradiated by environmentally significant wavelengths of light (HSDB, 2005). Aqueous hydrolysis does not play an important role in the environmental fate of cyfluthrin. Hydrolysis half-lives of 231 days and 2 days were identified at pH 7 and 8, respectively (ATSDR, 2003). Cyfluthrin has a high potential to bioconcentrate in aquatic organisms (HSDB, 2005).

HUMAN HEALTH EFFECTS

ACUTE EXPOSURE

Effects/Symptoms

Limited data are available on the acute toxicity of cyfluthrin in humans, because pyrethroid poisonings are uncommon. Cases of acute occupational or accidental exposure to pyrethroids resulted in burning, itching, and tingling of the skin which resolved after several hours. Reported systemic symptoms included dizziness, headache, anorexia, and fatigue. Vomiting occurred most commonly after ingestion of pyrethroids. Less commonly reported symptoms included tightness of the chest, paresthesia, palpitations, blurred vision, and increased sweating. In serious cases, coarse muscular fasciculations (twitching), convulsions, and coma were reported (IPCS, 1997). Cyfluthrin is of low toxicity to humans largely due to its poor absorption from the bloodstream and rapid breakdown and excretion. Acute effects of cyfluthrin exposure in humans consist primarily of immediate or delayed skin irritation and immediate eye irritation. Itching, burning, and stinging

of exposed skin can progress to cutaneous paresthesias, which can last up to 24 hours. Sweating, heat, and water can make dermal symptoms worse (WHO, 2004; EXTOXNET, 1998; HSDB, 2005; IPCS, 1997).

As a pyrethroid, cyfluthrin inhibits cholinesterase (HSDB, 2005), and symptoms of acute toxicity in animals may include irritability, excessive salivation, uncoordinated gait, tremors, convulsions, and death (HSDB, 2005; EXTOXNET, 1998). Cyfluthrin is a type II pyrethroid, a class which is known to produce a complex poisoning syndrome involving a progressive development of symptoms. In rats, this manifests as burrowing behavior, coarse tremors, clonic seizures, sinuous writhing, and profuse salivation without lacrimation (HSDB, 2005). Nervous system effects have been reported in acute high-dose exposures of animals to cyfluthrin by oral routes (EXTOXNET, 1998). Neurological effects (e.g., disturbed posture, abnormal motor activity, restlessness, and agitated gate) have also been seen following acute inhalation exposures (ATSDR, 2003). Neurological symptoms following daily dermal doses of $\geq$ 1,845 mg/kg in rats for up to 7 days included pawing and whole body tremors (ATSDR, 2003).

The vehicle used in formulating cyfluthrin significantly affects its toxicity (WHO, 2004). Reported LD_{50} values range from 16 to 1,189 mg/kg body weight, depending on the vehicle used (WHO, 2004). The reported oral LD_{50}s range from 500 to 1,271 mg/kg in rats, 1,401 to 609 mg/kg in mice, greater than 100 mg/kg in dogs, greater than 1,000 mg/kg in rabbits, and greater than 1,000 mg/kg in sheep (EXTOXNET, 1998; HSDB, 2005).The oral LD_{50}s for cyfluthrin in polyethylene glycol and xylene are 500 and 270 mg/kg, respectively (HSDB, 2005), while the oral LD_{50} for a 5 percent water emulsion preparation is reported as 2,100 mg/kg body weight in rats (WHO, n.d.). Inhalation exposures in rats have resulted in 4-hour LC_{50}s ranging from 469 to 592 µg/L and a reported 1-hour LC_{50} greater than 1,089 µg/L (EXTOXNET 1998). The 4-hour LC_{50}s for aerosol and dust exposures in rats are reported as 0.1 mg/L and 0.53 mg/L, respectively (HSDB, 2005). Cyfluthrin is not considered highly toxic via the dermal route of exposure, with a dermal LD_{50} of greater than 5,000 mg/kg in rats (EXTOXNET, 1998; HSDB, 2005). Additionally, it is not a dermal sensitizer or irritant in guinea pigs and rabbits (WHO, 2004; EXTOXNET, 1998; HSDB, 2005) but did induce eye irritation in rabbits (WHO, 2004; HSDB, 2005).

Treatment

Cyfluthrin and its metabolites can be detected in blood and urine; however, the methods are not practical given how quickly these compounds are broken down in the body (ATSDR, 2003). There are no antidotes for cyfluthrin exposure. Treatment depends on the symptoms of the exposed person. If a person exhibits signs of typical pyrethroid toxicity following cyfluthrin exposure (nausea, vomiting, shortness of breath, tremors, hypersensitivity, weakness, burning, or itching), they should immediately remove any contaminated clothing. Any liquid contaminant on the skin should be soaked up and the affected skin areas cleaned with alkaline soap and warm water. Eye exposures should be treated by rinsing with copious amounts of 4 percent sodium bicarbonate or water. Contact lenses should be removed. Vomiting should not be induced following ingestion exposures, but the mouth should be rinsed. The person should be kept calm and medical attention should be sought as quickly as possible. Medical personnel will treat severe intoxications with a sedative and anticonvulsant. Ingestion of large amounts of cyfluthrin should be treated with gastric lavage using a 5 percent bicarbonate solution followed by powdered activated charcoal. Skin irritation may be treated with a soothing agent; exposure to light should be avoided (PAN, 2005; HSDB, 2005).

CHRONIC EXPOSURE

NONCANCER ENDPOINTS

Little data are available for humans following chronic exposures to cyfluthrin, although it is not likely to cause long-term problems when used under normal conditions (ATSDR, 2003). Available animal data suggest that chronic toxicity is highest by inhalation exposure, with lower toxicity by oral exposure. Dermal exposure has

the lowest chronic toxicity (WHO, 2004). Cyfluthrin does not appear to be a reproductive or developmental toxin in animals (HSDB, 2005; WHO, 2004; ATSDR, 2003; EXTOXNET, 1998; WHO/FAO, 1997). However, treatment-related reductions in viability, decreased lactation, and deceased birth weight or weight gain were observed in one 3-generation rat study (ATSDR, 2003; EXTOXNET, 1998; U.S. EPA, 2005b). No developmental or teratogenic effects were observed in several animal studies (HSDB, 2005; EXTOXNET 1998; U.S. EPA, 2005b). In a 1-year dog feeding study, high doses of cyfluthrin caused slight ataxia, increased vomiting, and increased pasty or liquid feces. Decreased body weights were seen in males (U.S. EPA, 2005b). Cyfluthrin does not show any mutagenic potential (HSDB, 2005; WHO, 2004; EXTOXNET, 1998; WHO/FAO, 1997). Decreased weight gain and organ weight changes secondary to body weight are the only significant effects observed in long-term feeding studies in rats, mice, and dogs (WHO/FAO, 1997; EXTOXNET, 1998; U.S. EPA, 2005b). Additionally, reversible damage to the sciatic nerve was observed (EXTOXNET, 1998).

CANCER ENDPOINTS

No evidence of carcinogenic potential has been reported in rats and mice exposed to cyfluthrin (WHO, 2004; EXTOXNET, 1998; WHO/FAO, 1997).

TOXICOKINETICS

Pyrethroids are rapidly absorbed via inhalation as is indicated by the excretion of their metabolites within 30 minutes of exposures. In workers, plasma cyfluthrin levels confirmed absorption. Oral exposure to pyrethroids results in absorption from the gastrointestinal tract. Cyfluthrin metabolites were identified in the urine of an orally exposed volunteer. Minimal oral absorption was estimated based on the recovery of urinary cyfluthrin metabolites (ATSDR, 2003).

As with other synthetic pyrethroids, biotransformation in mammals exposed to cyfluthrin occurs through hydrolysis of the central ester bond, oxidative attacks at several sites, and conjugation reactions that produce water-soluble metabolites that are excreted in urine and feces. For cypermethrin, the rapid hydrolytic cleavage of the ester bond is followed by oxidation, which results in carboxylic acid derivatives and phenoxybenzoic acid derivatives that are then excreted as alcohols; phenols; carboxylic acids; and their glycine, sulfate, glucuronide, or glucoside conjugates (ATSDR, 2003). The metabolism of cyfluthrin is biphasic with a rapid initial phase and a slower second phase. This is demonstrated by the elimination of 60 percent of an intravenous dose within the first 24 hours followed by 6 percent elimination during the second 24 hours. Similarly, in feces 20 percent was eliminated on the first day and 3 to 4 percent was eliminated on the second day. Additionally, a single oral dose of cyfluthrin was shown to be 98 percent eliminated within 48 hours (EXTOXNET, 1998). Inhalation of a single dose of cyfluthrin in humans resulted in urinary metabolites within 30 minutes of exposure (ATSDR, 2003; WHO/FAO, 1997).

Elimination of cyfluthrin following inhalation exposure follows first-order kinetics with 93 percent of the dose being excreted within 24 hours of exposure. The elimination half-times for cis-/trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (DCCA) and, 4-fluoro-3-phenoxybenzoic acid (FPBA) metabolites and their isomers range from 5.3 to 6.9 hours and remain constant over a range of exposure levels (ATSDR, 2003). Based on occupational human exposure studies, the elimination half-time for cyfluthrin is estimated at 0.5 to 2 hours for plasma and 5 hours for urine (ATSDR, 2003). Oral exposures to cyfluthrin resulted in approximately 60 to 70 percent of the dose being eliminated in the urine and the rest eliminated in the feces (WHO/FAO, 1997).

ECOLOGICAL EFFECTS

ACUTE EXPOSURE

Toxicity in Non-Targeted Terrestrial Organisms

Cyfluthrin has a very low toxicity in birds (EXTOXNET, 1998; HSDB, 2005). Oral LD_{50} values range from greater than 2,000 mg/kg in acute tests in bobwhite quail to greater than 5,000mg/kg in subacute tests in mallards and bobwhite quail (EXTOXNET, 1998). Other reported oral LD_{50}s are 4,500 to greater than 5,000 mg/kg in hens (depending on the vehicle used), greater than 2,000 mg/kg in Japanese quail, and 250 to 1,000 mg/kg in canaries (EXTOXNET, 1998; HSDB, 2005). As with other pyrethroid insecticides, cyfluthrin is extremely toxic to honey bees in laboratory tests. The reported LD_{50} is 0.037 mg/bee (EXTOXNET, 1998). However, in the field, serious adverse effects have not been seen due to low application rates and low environmental persistence (HSDB, 2005). Cyfluthrin is also highly toxic to other beneficial insects (EXTOXNET, 1998) but of low toxicity to earthworms (WHO, 2004).

Toxicity in Non-Targeted Aquatic Systems

As with other pyrethroids, cyfluthrin is very toxic to marine and freshwater fish and invertebrates (EXTOXNET, 1998; WHO, 2004). The high toxicity in fish is illustrated by the low exposures that cause lethality. The reported 48-hour LC_{50} for rainbow trout is 0.00068 mg/L, while in bluegill, carp, and golden orfe, the reported LC_{50}s are 0.0015, 0.022, and 0.0032 mg/L, respectively. In sheepshead minnow, an LC_{50} of 0.004 mg/L is reported (EXTOXNET, 1998). The 96-hour LC_{50} values range from 28 ng/L in bluegill sunfish to 330.9 ng/L in golden orfe (HSDB, 2005). In marine and estuarine invertebrates, extreme sensitivity to cyfluthrin is also seen. Reported LC_{50}s include 2.42 ng/L for mysid shrimp. An EC_{50} of 3.2 ng/L was seen in eastern oysters (EXTOXNET, 1998). Cyfluthrin has a high potential to bioconcentrate in aquatic organisms based on the measured BCF of the structurally similar insecticide cypermethrin (HSDB, 2005).

CHRONIC EXPOSURE

Due to low rate of application and low persistence of cyfluthrin in both terrestrial and aquatic environments, serious adverse effects are not anticipated from chronic exposures (HSDB, 2005).

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PROFILE FOR DDT:

CAS REGISTRY NUMBER 50-29-3

SUMMARY

CHEMICAL HISTORY

Dichlorodiphenyltrichloroethane (DDT) is a broad range pesticide used since the late 1930s on agricultural crops and to control disease-carrying insects, such as those that spread malaria and typhus. In 1955, a global campaign to eradicate malaria was adopted based on the use of DDT, and endemic malaria in developed countries, subtropical Asia, and Latin America was eradiated by 1967. However, few African countries participated, and the campaign ended in 1969 due to lack of support and developing mosquito resistance to DDT (Rogan and Chen, 2005). DDT was banned in the United States and other industrialized countries in the early 1970s, largely due to its persistence in the environment. However, DDT is still in use today in sub-Saharan African countries to control malaria (ATSDR, 2002). DDT is not generally thought to be toxic to humans; however, recent data have indicated that exposure to DDT in amounts necessary for malaria control may cause preterm birth and early weaning (Rogan and Chen, 2005). Acute exposure to high levels of DDT by any route causes neurological effects, including excitability, headache, nausea, vomiting, and dizziness (ATSDR, 2002).

Data on Mexican workers who use DDT show very high levels of DDT in adipose (fat) tissues and serum (Rogan and Chen, 2005). Children are also at risk for increased exposure to DDT and its metabolites via consumption of breast milk and cow's milk. DDT exhibits its toxic effects in humans on the nervous system and liver (ATSDR, 2002).

DESCRIPTION OF DATA QUALITY AND QUANTITY

EPA and ATSDR have developed quantitative human heath benchmarks (EPA's chronic RfD and oral and inhalation CSFs and ATSDR's acute and intermediate oral MRLs). Several comprehensive reviews on the toxicity of DDT are available and recommended:

- Toxicological Profile for DDT, DDE, and DDD (ATSDR, 2002)
- IRIS summary review (U.S. EPA, 2005a)
- A recent review article by Rogan and Chen (2005).

Other relevant resources include

- Specifications for Pesticides Used in Public Health (WHO, 1999)
- Environmental Health Criteria 9: DDT and its Derivatives (IPCS,1979)
- Pesticide Information Profile for DDT (EXTOXNET, 2003)
- The Pesticide Action Network (PAN) Pesticide Database (PAN, 2005).

SUMMARY TABLE

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute	Inhalation	0.0005	mg/kg/day	Adopt acute oral MRL as acute inhalation; assume no portal of entry effects	
Intermediate	Inhalation	0.0005	mg/kg/day	Adopt intermediate oral MRL as intermediate inhalation; assume no portal of entry effects	
Chronic	Inhalation	0.0005	mg/kg/day	Adopt chronic RfD as chronic inhalation; assume no portal of entry effects	
Cancer	Inhalation	0.034	per mg/kg/day	Inhalation CSF (calculated from oral data) for benign and malignant liver tumors in rats and mice	U.S. EPA (1997)
Acute	Oral	0.0005	mg/kg/day	Acute oral MRL based on neurodevelopmental effects in mice	ATSDR (2002)
Intermediate	Oral	0.0005	mg/kg/day	Intermediate oral MRL based on liver effects in rats	ATSDR (2002)
Chronic	Oral	0.0005	mg/kg/day	Chronic oral RfD based on liver effects in rats	U.S. EPA (2005a)
Cancer	Oral	0.034	per mg/kg/day	Oral CSF for benign and malignant liver tumors in rats and mice	U.S. EPA (2005a)
Acute	Dermal	0.0005	mg/kg/day	Adopt acute oral MRL as acute dermal; assume no first pass effects and 100% oral absorption	
Intermediate	Dermal	0.0005	mg/kg/day	Adopt intermediate oral MRL as intermediate dermal; assume no first pass effects and 100% oral absorption	
Chronic	Dermal	0.0005	mg/kg/day	Adopt chronic RfD as chronic dermal; assume no first pass effects and 100% oral absorption	
Cancer	Dermal	0.034	per mg/kg/day	Adopt oral CSF as chronic dermal; assume no first pass effects and 100% oral absorption	

For oral exposure, the acute oral MRL of 0.0005 mg/kg/day was derived for DDT based on the LOAEL for neurodevelopmental effects in mice perinatally exposed to DDT (ATSDR, 2002). The intermediate oral

MRL of 0.0005 mg/kg/day was derived for DDT based on the NOAEL for liver effects in rats exposed to DDT in the diet (ATSDR, 2002). A chronic RfD of 0.0005 mg/kg/day was derived for DDT based on liver lesions in male and female rats exposed to DDT in the diet for 27 weeks. An oral CSF of 3.4E-1 per mg/kg/day was also derived based on benign and malignant liver tumors in male and female rats and mice chronically exposed to DDT in the diet (U.S. EPA, 2005a).

For inhalation exposure, no noncancer toxicity factors were derived for DDT because adequate experimental data do not exist for this route (ATSDR, 2002; U.S. EPA, 2005a). An inhalation unit risk of 9.75E-5 per $\mu g/m^3$ and an inhalation cancer slope factor of 3.4E-1 per mg/kg/day were calculated from oral data for benign and malignant liver tumors in male and female rats and mice chronically exposed to DDT in the diet (U.S. EPA, 2005a).

For dermal exposure, no dermal toxicity factors have been derived because EPA and ATSDR have not yet identified a method suitable for this route of exposure. However, EPA has developed a simplified paradigm for making route-to-route extrapolations for systemic effects via percutaneous absorption in which complete oral absorption is assumed, thereby eliminating the need to adjust the oral toxicity value (U.S. EPA, 2004). This approach may result in underestimating risk. No adjustment was made and oral toxicity values were used for the dermal assessment.

BACKGROUND

CASRN:	50-29-3
Synonyms:	(p-chlorophenyl)ethane; dichlorodiphenyl trichloroethane; DDT; 1,1'-(2,2,2-trichloroethylidene)bis(4-chlorobenzene); α-α-bis(p-chlorophenyl)-β, β, β –trichloroethane (ATSDR, 2002)
Chemical Group:	organochlorine (ATSDR, 2002)
Registered Trade Names:	Genitox, Anofex, Detoxan, Neocid, Gesarol, Pentachlorin, Dicophane, Chlorophenothane (ATSDR, 2002) Cesarex, p,p'-DDT, Dichlorodiphenyltrichloroethane, Dinocide, Didimac, Digmar, ENT 1506, Guesapon, Guesarol, Gexarex, Gyron, Hildit, Ixodex, Kopsol, Neocid, OMS 16, Micro DDT 75, Rukseam, R50 and Zerdane (EXTOXNET, 2003).

USAGE

DDT is a broad spectrum insecticide that was once widely used. In World War II, it was used extensively to control insect-borne diseases such as malaria and typhus. In the early 1970s, it was banned in the United States and most industrial countries due to its persistence in the environment. Today it is used only in sub-Saharan Africa and in emergency cases to control malaria (ATSDR, 2002).

FORMULATIONS AND CONCENTRATIONS

Technical grade DDT is generally used as an insecticide. It is made up of three isomers of DDT, including p,p'-DDT (up to 85 percent), o,p'-DDT (15 percent), and o,o-DDT (trace amounts) (ATSDR, 2002). DDT is available as an aerosol, a dustable powder, an emulsifiable concentrate, in granules, or as wettable powders (EXTOXNET, 2003). DDT that is used for indoor residual spraying is usually a wettable powder that has 75 percent active ingredient. WHO (1999) indicated that the content of p,p'-DDT in the DDT formulation should be declared and contain the following:

- Technical grade DDT: no less than 700 g/kg p,p'-DDT
- Dustable powder: over 25–100 g/kg p,p'-DDT with a permitted tolerance of +/- 10% of the declared content
- Wettable powder: 100–250 g/kg p,p'-DDT with a permitted tolerance of +/- 6% of the declared content, or 250–500 g/kg p,p'-DDT with a permitted tolerance of +/- 5% of the declared content, or greater than 500 g/kg with a permitted tolerance of +/- 25 g/kg.

SHELF LIFE

DDT has a long shelf life. It is resistant to destruction by light or oxidation (HSDB, 2005).

DEGRADATION PRODUCTS

DDT breaks down very slowly by dehydrohalogenation into DDE [1,1-dichloro-2,2-bis(p-dichlorodiphenyl)ethylene] and DDE [1,1-dichloro-2,2-bis(p-chlorophenyl)ethane]. In animal systems, these metabolites are stored in body fat and either leave the body slowly if exposure decreases, remain constant in the tissues, or increase with continued exposures (ATSDR, 2002). Stored DDE and DDD are slowly transformed to DDA [bis(dichlorodiphenyl) acetic acid] by other metabolites. DDA and its metabolites are then excreted in the urine (EXTOXNET, 2003).

ENVIRONMENTAL BEHAVIOR

FATE AND TRANSPORT IN TERRESTRIAL SYSTEMS

DDT and its metabolites are highly persistent and bioaccumulate in the environment (ATSDR, 2002). The persistence of DDT in the environment is mainly due to its being soluble in fat and virtually insoluble in water (IPCS, 1979). DDT is released into the air as a result of spraying operations in countries where it is still being used. DDT and its metabolites may also enter the air when they evaporate from contaminated soil and water. They may then be deposited back onto land and surface waters. This cycle of volatilization and deposition may be repeated numerous times resulting in the movement of DDT in the atmosphere. As a result, DDT and its metabolites have been found in air, sediment, and snow, and accumulated in biota in the Arctic and Antarctic regions. As a result of this ability to undergo long-range global transport, the actual lifetime of DDT and its metabolites is substantially longer than indicated by their estimated half-lives. In the atmosphere, DDT and its metabolites occur as a vapor or are attached to particulates in the air. As a vapor, DDT and its metabolites are broken down by sunlight. DDT is also broken down slowly by microorganisms (ATSDR, 2002).

In most soils, DDT is practically immobile due to its strong affinity to soil, especially organic soil matter (EXTOXNET, 2003). Because DDT and its metabolites (DDD and DDE) stick strongly to the soil, they remain mostly in the surface layers of soil. Soil with DDT bound to it may enter waterways via runoff (ATSDR, 2002). Other routes of loss and breakdown of DDT in soil include volatilization, photolysis, and aerobic and anaerobic biodegradation. Loss from volatilization depends on how much DDT was applied, the amount of organic material in the soil, proximity to the soil-air interface, and the amount of sunlight (EXTOXNET, 2003). Very little DDT will seep into groundwater. The persistence of DDT is soil varies with the type of soil, temperature, and soil mositure (ATSDR, 2002). The typical half-life of DDT in soil ranges from 2 years to 15 years (EXTOXNET, 2003). DDT and its metabolites last for a shorter time in soils that contain more microorganisms, wet soils, and warmer soils (ATSDR, 2002). Because DDT persists in the soil, bioaccumulation in plants has been observed, especially in the root.

FATE AND TRANSPORT IN AQUATIC SYSTEMS

The two main ways that DDT may be released into surface waters are by direct application for the control of mosquito-borne malaria and by runoff from sprayed areas. Atmospheric transport and drift represent lesser scenarios (EXTOXNET, 2003). DDT is a highly persistent compound with low volatility and low solubility in water, leading to great potential to bioaccumulate in the environment. DDT binds to particles in surface water, settles, and then deposits in the sediment (ATSDR, 2002). Studies have shown that DDT dose not readily break down in estuary sediments. Additionally, DDT has been widely detected in ambient surface water samples in the United States. The reported half-life of DDT in lake and river water is 56 and 28 days, respectively; the half-life in river water is shorter because river water usually has more organic soil matter (EXTOXNET, 2003). The main fate processes in the aquatic environment are volatilization, photodegradation, absorption to water-borne particles, and sedimentation, with the dominant fate process being volatilization. In surface waters, DDT is transformed via biotransformation and photolysis (ATSDR, 2002). DDT is also readily taken up by and accumulates in aquatic organisms (EXTOXNET, 2003).

HUMAN HEALTH EFFECTS

ACUTE EXPOSURE

Effects/Symptoms

DDT has been used in large populations for more than 60 years with little acute toxicity except from accidental exposures (Rogan and Chen, 2005). DDT impairs the conduction of nerve impulses. In humans, this can cause effects ranging from mild altered sensations to tremors, convulsions, and respiratory depression (ATSDR, 2002). Additional effects observed in humans following acute DDT exposure include headaches; nausea; vomiting; diarrhea; numbness; paresthesia; increased liver enzyme activity; irritation of the eyes, nose, or throat; altered gait; and malaise or excitability (EXTOXNET, 2003; PAN, 2005).

The toxicity of DDT varies with formulation and the exposure pathway. In humans, the oral route is thought to be the most significant. Fatalities have been documented following ingestion of commercial preparations that also contain substances other than DDT (ATSDR, 2002). Children appear to be more susceptible to the fatal effects of DDT than adults (EXTOXNET, 2003). Dermal and inhalation exposures to DDT are more likely in humans if the compound is in solution form (dermal) or aerosol form (inhalation). Exposure through dermal contact is more likely when DDT is in an oily solution than when it is in a wettable powder form, which is the formulation used most often in indoor residual spraying (ATSDR, 2002).

In animals, the toxicity DDT and its analogues have been studied extensively. Acute exposure to high doses of DDT can cause death, with the toxicity dependent upon the formulation. Acute oral LD_{50} values range from 150 to 200 mg/kg in mice, 113 to 800 mg/kg in rats, and 500 to 750 mg/kg in dogs (EXTOXNET, 2003). Deaths were usually a result of respiratory arrest (ATSDR, 2002). DDT is most known for its neurotoxic effects in animals. Similar to its effects in humans, DDT causes hyperactivity, tremor, and seizures in animals. Acute exposure to low doses of DDT can cause subtle neurodevelopmental effects in neonatal mice (EXTOXNET, 2003). Liver effects such as increased liver weights, induction of liver enzymes, and hepatic-cell hypertrophy and necrosis have also been observed (Rogan and Chen, 2005). Because of the hormone altering action of DDT isomers, reproductive and developmental effects have also been seen in laboratory animals. Acute exposure to DDT and its metabolites in food may have negative effects on reproduction (ATSDR, 2002). DDT is very slightly toxic to laboratory animals via acute dermal exposure. LD_{50} values range from 2,500 to 3,000 mg/kg in rats, 1,000 mg/kg in guinea pigs, and 300 mg/kg in rabbits. Acute inhalation exposure of animals to DDT does not result in significant absorption in the lungs (EXTOXNET, 2003).

Treatment

Exposure to DDT may be measured through laboratory tests. DDT and its metabolites (DDE and DDD) may be detected in the blood/plasma, semen, urine, liver, kidney, fatty tissue, skin lipids, breastmilk, and lymphatic tissues (ATSDR, 2002). DDT exposure should be treated with anticonvulsants (benzodiazepines), oxygen, and cardiopulmonary monitoring. Epinephrine, other adrenergic amines, atropine, and orally administered fats are all contraindicated (PAN, 2005; Reigart and Roberts, 1999).

CHRONIC EXPOSURE

NONCANCER ENDPOINTS

Most chronic exposure human data come from studies of workers who are exposed to DDT in manufacturing facilities or as spray applicators and from epidemiological studies. These studies indicate that chronic oral exposure to small amounts of DDT does not produce toxic effects in humans. However, DDT and its metabolite DDE may alter hormonally mediated endpoints such as lactation duration, maintenance of pregnancy, and fertility. Increased chances of premature birth, infants that are small for their gestational age, and height abnormalities in children have also been associated with high DDE levels in the blood (ATSDR, 2002). DDT and its metabolites affect male reproductive parameters such as semen volume, sperm count, testosterone ratios, and sperm DNA damage (Rogan and Chen, 2005).

In animals, liver effects have been seen following chronic exposure to moderate levels of DDT (ATSDR, 2002). The main effect was localized liver damage. Additional chronic effects in animals include nervous system (tremors, central nervous system cellular chemistry changes, loss of equilibrium), kidneys (adrenal gland and kidney damage), and immune system (reduced antibody formation, reduced immune cells). Those effects were seen at levels much higher than than expected human exposure levels (EXTOXNET, 2003).

CANCER ENDPOINTS

IARC has classified DDT in group 2B; a probable human carcinogen (IARC, 1991). EPA has also determined that DDT is a probable human carcinogen (U.S. EPA, 2005a). The available epidemiological evidence regarding carcinogenicity in humans is inconclusive. A slight increase in risk from lung cancer was observed in workers at two DDT production facilities. No other cancer incidences were found in sufficient numbers for analysis. Inconsistent results have been found when comparing serum DDT/DDE levels in people with and without cancer (IARC, 1991). One study indicated a potential link between chronic, high dose DDT exposure and pancreatic cancer in chemical workers but the reliability of the study is questionable. The association between p,p'-DDE and breast cancer has been studied extensively, but studies have failed to show an association (Rogan and Chen, 2005). Studies have indicated that DDT and its metabolites are not mutagenic (ATSDR, 2002). In animals, DDT has been shown to cause liver and lung cancers (ATSDR, 2002).

TOXICOKINETICS

DDT is absorbed via inhalation, the gastrointestinal tract, and dermally. In humans, oral exposure to DDT is considered the most significant. Orally, DDT is absorbed from the gastrointestinal tract into the lymphatic system. There is also some absorption into the portal blood. Distribution of DDT to all body tissues then occurs from the lymphatic system and blood. In the tissues, DDT is stored in proportion to the lipid (fat) content of the tissue (ATSDR, 2002). DDT is initially metabolized into DDE and DDD, however these are ultimately transformed into DDA (EXTOXNET, 2003). DDA and its metabolites are eventually excreted in the urine. DDT may also be excreted via feces, semen, and breastmilk (ATSDR, 2002).

ECOLOGICAL EFFECTS

ACUTE EXPOSURE

DDT is only slightly toxic to birds. Acute oral LD_{50} values in various bird species include the following: Japanese quail (841 mg/kg), pheasant (1,334 mg/kg), and mallard (2,240 mg/kg). Most avian exposures are a result of the food chain and consumption of aquatic (e.g., fish) or terrestrial (e.g., earthworms or other birds) species that have an accumulated body burden of DDT. However, earthworms are not susceptible to the acute toxic effects of DDT. Additionally, DDT is not toxic to bees. DDT may, however, be toxic to bats as DDT may be released from fat stores during migration (EXTOXNET, 2003).

DDT is highly toxic to many aquatic species. On average, acute exposure to DDT is only slightly toxic to amphibians and phytoplankton; moderately toxic to annelida, mollusks, and zooplankton; highly to very highly toxic to fish; and very highly toxic to crustaceans (PAN, 2005). In fish, the 96-hour LC_{50} values range from 1.5 µg/L in northern pike to 21.5 µg/L in fathead minnows. DDT is very highly toxic to stoneflies, midges, crayfish, sow bugs, and other aquatic invertebrate with 96-hour LC_{50} values ranging from 0.18 to 7.0 µg/L. In aquatic invertebrates, DDT adult stages are less susceptible than developmental stages (EXTOXNET, 2003).

CHRONIC TOXICITY

Chronic exposure to DDT has been linked to reproductive effects in birds. Eggshell thinning and embryo death are two of the main concerns especially in birds of prey. The mechanism of eggshell thinning is thought to be from the major metabolite DDE. Additionally, the reproductive behavior of birds may also be subtlety altered by DDT and DDE exposure. In laboratory studies, changes in courtship behavior, delays in pairing and egg laying, and decreases in egg weight have been observed in some bird species, though it is not clear what these effects mean for the survival of wild bird species. A synergism may exist between DDT metabolites and organophosphate pesticides to produce greater neurotoxicity and increased deaths (EXTOXNET, 2003).

Chronic exposure to DDT may occur in fish and aquatic species through bioaccumulation. This occurs from the uptake of DDT in sediments and water, with smaller fish taking up higher amounts of DDT. It has been estimated that the half-time elimination of DDT for rainbow trout is 160 days. Bioaccumulation can occur at very low environmental concentrations and the bioconcentration factor for DDT is 1,000 to 1,000,000, depending on the aquatic species (EXTOXNET, 2003).

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PROFILE FOR DELTAMETHRIN:

CAS REGISTRY NUMBER 52918-63-5

SUMMARY OF INSECTICIDE

CHEMICAL HISTORY

Deltamethrin is a broad spectrum synthetic pyrethroid insecticide used in agricultural and human health applications. It was first marketed in 1977 (IPCS, 1990; EXTOXNET, 1995; WHO/FAO, 2001) and has been in use longer than any alpha-cyano pyrethroid with an excellent safety record (WHO/FAO, 1999). It is similar to the natural insecticide pyrethrum, which comes from chrysanthemums; however, it is more effective and longer lasting (EXTOXNET, 1995; WHO/FAO, n.d.; IPCS, 1990). Deltamethrin is considered the most powerful synthetic pyrethroid (EXTOXNET, 1995). For mosquito control, it is used on bed nets and other materials that are dipped in deltamethrin to protect the user (Barlow et al., 2001; EXTOXNET, 1995; WHO/FAO, 2001). Deltamethrin is typically formulated as emulsifiable concentrates, wettable powders, ultra-light-volume (ULV) and flowable formulations, and granules either alone or combined with other pesticides (EXTOXNET, 1995; IARC, 1991). A dispersible tablet is also used to treat mosquito nets (Barlow et al., 2001). Deltamethrin is of moderate toxicity to mammals because metabolizes rapidly and does not accumulate (WHO/FAO, n.d.; WHO/FAO, 1999). It is of low risk to humans when used at levels recommended for its designed purpose (ATSDR, 2003; WHO, 2004). General population exposures are expected to be very low and to occur mostly through public health uses and dietary residues. As a synthetic pyrethroid, deltamethrin exhibits its toxic effects by interfering with the way the nerves and brain normally function. Typical symptoms of acute exposure are irritation of skin and eyes, severe headaches, dizziness, nausea, anorexia, vomiting, diarrhea, excessive salivation, and fatigue. Tremors and convulsions have been reported in severe poisonings. Inhaled deltamethrin has been shown to cause cutaneous paraesthesia (a burning, tingling, or stinging). However, these effects are generally reversible and disappear within a day of removal of the exposure (Barlow et al., 2001; WHO, 2004; ATSDR, 2003; IPCS, 1989, 1990). In animals, the critical effect is neurotoxicity (WHO, 2004).

DESCRIPTION OF DATA QUALITY AND QUANTITY

Adequate dose-response studies on the toxicity of deltamethrin exist for oral, dermal, and inhalation exposures. Most are oral exposure studies (WHO, 2004). Several comprehensive reviews on the toxicity of deltamethrin have been prepared or updated in recent years:

- Environmental Health Criteria 97: Deltamethrin (IPCS, 1990)
- Health and Safety Guide No. 30: Deltamethrin Health and Safety Guide (IPCS, 1989)
- A review article by Barlow et al. (2001)
- Pesticide Information Profiles (PIP) for Deltamethrin (EXTOXNET, 1995)
- Data Sheets on Pesticides No. 50—Deltamethrin (WHO/FAO, n.d.)
- A Generic Risk Assessment Model for Insecticide Treatment and Subsequent Use of Mosquito Nets (WHO, 2004)
- Malaria Vector Control—Insecticides for Indoor Spraying (WHO/FAO, 2001)

EPA has developed quantitative human health benchmarks (acute and chronic oral RfDs, intermediate-term oral, and short-, intermediate-, and long-term dermal and inhalation benchmarks) for deltamethrin.

SUMMARY TABLE

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute, Intermediate, Chronic	Inhalation	0.01	mg/kg/day	Oral NOAEL for clinical signs in dogs at 1 mg/kg/day with UF of 100 applied	U.S. EPA (2004)
Acute	Oral	0.01	mg/kg/day	Acute RfD based on neurological effects in rats	U.S. EPA (2004)
Intermediate	Oral	0.01	mg/kg/day	Oral NOAEL for clinical signs in dogs at 1 mg/kg/day with UF of 100 applied	U.S. EPA (2004)
Chronic	Oral	0.01	mg/kg/day	Chronic RfD based on clinical signs in dogs	U.S. EPA (2004)
Acute, Intermediate, Chronic	Dermal	10	mg/kg/day	Dermal NOAEL of 1000 mg/kg/day in rats with a UF of 100 applied	Barlow et al. (2001)

For oral exposure, an acute RfD of 0.01 mg/kg/day was derived based on a NOAEL of 1 mg/kg/day for neurological effects (reduced motor activity) observed in rats exposed to deltamethrin (Crofton et al., 1995), with an uncertainty factor of 100 applied to account for interspecies and intrahuman variability (U.S. EPA, 2004). A chronic oral RfD of 0.01 mg/kg/day was derived based on a NOAEL of 1 mg/kg/day for clinical signs and reduced weight gain in dogs (study citation not provided), with an uncertainty factor of 100 applied (U.S. EPA, 2004). The chronic RfD is appropriate to use for intermediate-term exposures (U.S. EPA, 2004).

For inhalation exposures, the chronic RfD is also appropriate for short-, intermediate-, and long-term exposures (U.S. EPA, 2004).

For dermal exposure, a NOAEL of 1,000 mg/kg/day was identified in rats dermally exposed to deltamethrin for 21 days (study citation not provided). An uncertainty factor of 100 was applied to account for interspecies and intrahuman variability, for a dermal benchmark value of 10 mg/kg/day. This value is appropriate for all dermal exposure durations (Barlow et al., 2001). The large difference between the oral and dermal NOAELs is due to rapid absorption of deltamethrin from the gastrointestinal tract versus low dermal absorption (WHO, 2004; Barlow et al., 2001).

INSECTICIDE BACKGROUND

CASRN:	52918-63-5
Synonyms:	cyano(3-phenoxy-phenyl)methyl;2-(2,2dibromoethenyl)-2,2-dimethylcyclopropanecarboxylate (CA); alpha-cyano-m-phenoxybenzyl,(1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropanl-carboxylate, (S)-alpha-cyano-3-phenoxybenzyl (1R)-cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-carboxylate, decamethrine, FMC 45498, NRDC 161, OMS 1998, RU 22974, RUP 987 (EXTOXNET, 1995; IARC, 1991; WHO/FAO, n.d.).
Chemical Group:	pyrethroid (PAN, 2005)

Registered Trade Names:	Products containing deltamethrin (NRDC 161 and RU 22974): Butoflin, Butoss, Butox, Cislin, Cislin 2.5% EC, Cislin 2.5% WP, Cislin RTU, Crackdown, Cresus, Decis, Decis-Prime, K-Othrin, K-Orthine, K-Otek, Kordon, Sadethrin (EXTOXNET, 1995; WHO/FAO, n.d.; ATSDR, 2003; IPCS, 1989; IARC, 1991; FPA, 2002).

USAGE

Deltamethrin is used to combat pests on a variety of crops, including cotton, fruit, vegetables, coffee, maize, wheat, rapeseed, hops, and soybeans (ATSDR, 2003; EXTOXNET, 1995; IPCS, 1989, 1990). It is also used to control insects in stored grains, to protect cattle from infestation, and in public health applications. It may be applied to foods, field crops, gardens, orchards, and vineyards (WHO/FAO, n.d.). Public health uses include malaria control in Central America and Africa (IPCS, 1990). Deltamethrin belongs to the pyrethroid class of insecticides, which have long been used to control mosquitoes, human lice, beetles, and flies (ATSDR, 2003). For mosquito protection, it is used on bed nets and other materials that are dipped into the deltamethrin to protect the user. All concentrated formulations of deltamethrin were restricted by EPA due to its potential toxicity to aquatic organisms, and it may only be purchased and used by certified applicators (ATSDR, 2003).

FORMULATIONS AND CONCENTRATIONS

Deltamethrin is available in technical grade (> 98 percent pure), suspension concentrate, emulsifiable concentrate (25–100 g/L), ultra-low-volume (ULV) concentrate (1.5–30 g/L), wettable powder (25–50 g/kg), flowable powder (7.5–50 g/L), dust powder (0.525 g/kg), and granules (0.5 and 1.0 g/kg) alone or combined with other pesticides (IPCS, 1989, 1990; WHO/FAO, n.d.). Deltamethrin that is marketed for use as a bed net treatment comes in a single 400 mg tablet form (WHO, 2004).

SHELF LIFE

In storage conditions at 40°C, deltamethrin is stable to light, heat, and air for 6 months and to light and air for 2 years. It is most stable in acidic media and unstable in alkaline environments (EXTOXNET, 1995; IPCS, 1989, 1990; WHO/FAO, n.d.).

DEGRADATION PRODUCTS

Deltamethrin's major metabolites are free and conjugated Br_2CA, *trans*-hydroxymethyl-Br_2CA, and 3-(4-hydroxyphenoxy)benzoic acid formed by ester cleavage, oxidation, and conjugation (IPCS, 1990).

ENVIRONMENTAL BEHAVIOR

FATE AND TRANSPORT IN TERRESTRIAL SYSTEMS

Deltamethrin is not expected to be mobile in soil, with a Koc ranging from 46,000 to 1,630,000 (HSDB, 2005). Additionally, it binds tightly to soil particles, is insoluble in water, and has low application rates (IPCS, 1989, 1990). Volatilization is a major environmental fate process from moist soils but this is lessened by its adsorption to soil. Another major fate process is biodegradation, with a half-life of several weeks to greater than 100 days (HSDB, 2005). As with other synthetic pyrethroids, deltamethrin degrades rapidly in soil and plants (IPCS, 1990). Degradation occurs within 1 to 2 weeks for soil, and no residues remain on plants after 10 days (EXTOXNET, 1995). Deltamethrin does not bioaccumulate in terrestrial systems (IPCS, 1990).

FATE AND TRANSPORT IN AQUATIC SYSTEMS

Because deltamethrin binds tightly to soil and is practically insoluble in water, very little leaching into groundwater is expected. In pond water, deltamethrin was absorbed rapidly by sediment, uptake by plants, and evaporation (EXTOXNET, 1995). Volatilization is a major environmental fate process in surface waters but is lessened by soil adsorption. Deltamethrin breaks down quickly in water with reported half-lives of 2 to 4 hours. The estimated volatilization half-life in a model river is 30 hours, and in a model lake, 500 hours. In a model pond, the estimated volatilization half-life is 7 years if adsorption is considered. Deltamethrin has a high potential to bioconcentrate in aquatic organisms. It has an estimated bioconcentration factor of 270. The reported estimated hydrolysis half-life was 36 years at pH 7 and 3.6 years at pH 8 (HSDB, 2005).

HUMAN HEALTH EFFECTS

ACUTE EXPOSURE

Effects/Symptoms

There are limited data on the acute toxicity of deltamethrin in humans. Acute effects in humans include irritability, headache, salivation, sweating, fever, anxiety, rapid heart beat, diarrhea, dyspnea, tinnitus, runny nose, vomiting, edema, hepatic microsomal enzyme induction, peripheral vascular collapse, serum alkaline phosphatase elevation, tremors, ataxia, convulsions leading to muscle fibrillation and paralysis, and death due to respiratory failure (EXTOXNET, 1995; WHO/FAO, n.d.; IPCS, 1990). Dermatitis is expected after dermal exposures, which often occur as a result of inadequate handling safety precautions during agricultural use (EXTOXNET, 1995; IPCS, 1990). Coma was caused within 15 to 20 minutes at oral exposure levels of 100 to 250 mg/kg (EXTOXNET, 1995). Facial paraesthesia is a common indicator of exposure of humans to high levels (WHO/FAO, n.d.).

In clinical studies in humans, slight irritation but no skin damage was reported in patch tests of deltamethrin put on faces of volunteers (IPCS, 1990). Acute occupational exposures to deltamethrin have resulted mostly in dermal symptoms including itching, burning, and paraesthesia. These are an early, reversible signs of exposure and are due to local, not systemic, exposures (Barlow et al., 2001; IPCS, 1990; EXTOXNET, 1995). Neurological signs such as headaches, dizziness, fatigue, nausea, anorexia, transient EEG changes, muscular fasciculation, and convulsions have also been reported following acute occupational exposures (Barlow et al., 2001; EXTOXNET, 1995). Loss of consciousness, muscle cramps, myosis, and tachycardia were reported in a 13-year-old girl who attempted suicide by ingesting 5 g of deltamethrin (200 mL of a 2.5% EC formulation). After appropriate medical intervention, she recovered completely within 48 hours. Only digestive and hepatic signs were observed in a 23-year-old man who attempted suicide by ingesting 1.75 g of deltamethrin (70 mL of a 2.5% EC formulation) (IPCS, 1990).

Animal studies have indicated that deltamethrin has low acute toxicity; however, this varies greatly depending on the route of administration and the vehicle used (WHO, 2004; Barlow et al., 2001). In acute exposure studies, the mouse is the species most susceptible to deltamethrin toxicity (WHO/FAO, n.d.). Reported oral LD_{50} values range from 19 to 34 mg/kg in mice, 52 to over 5,000 mg/kg in male rats, 30 to 139 mg/kg in female rats, and over 300 mg/kg in dogs (EXTOXNET, 1995; IPCS, 1990; WHO/FAO, n.d.; WHO/FAO, 2001; Barlow et al., 2001). Following acute dermal exposure, the reported LD_{50} is greater than 2,940 mg/kg in rats and dogs and greater than 2,000 mg/kg in rabbits (EXTOXNET, 1995; IPCS, 1990; WHO/FAO, n.d.; WHO/FAO, 2001). The reported inhalation 6-hour LD_{50} in rats is 600 mg/m^3 (IPCS, 1990).

Hyperactivity and hypersensitivity are general characteristics of pyrethroid poisonings. However, the signs of acute deltamethrin poisoning are different from other pyrethroids in that it produces a unique set of effects that occur in a specific sequence in animals. They begin with chewing, pawing, and burrowing behavior;

excessive salivation; and coarse tremors advancing to choreoathetosis and sometimes terminal clonic seizures. Rolling convulsions are especially characteristic of deltamethrin poisoning (WHO/FAO, n.d.; EXTOXNET, 1995). In rabbits and guinea pigs, no primary skin irritation or sensitization was observed following acute dermal exposure to 0.5 g/animal, although transitory ocular irritation was seen in rabbits without immediate rinsing (EXTOXNET, 1995; WHO/FAO, n.d.). However, another study reported skin irritation in rats and guinea pigs (EXTOXNET, 1995). Cardiovascular effects include a rapid fall in blood pressure, severe bradycardia, and EKG changes in intravenously exposed dogs (WHO/FAO, n.d.)

Treatment

Deltamethrin and its metabolites can be detected in blood and urine; however, the methods are not practical given how quickly these compounds are broken down in the body (ATSDR, 2003; WHO/FAO, n.d.). Levels of the degradation products bromide, cyanide, and 3-phenoxybenzyl in urine may be useful indicators in cases of severe toxicity (WHO/FAO, n.d.).

There are no antidotes for deltamethrin exposure (IPCS, 1989; WHO/FAO, n.d.). Treatment depends on the symptoms of the exposed person. If a person exhibits signs of typical pyrethroid toxicity following deltamethrin exposure (nausea, vomiting, shortness of breath, tremors, hypersensitivity, weakness, burning, or itching), they should immediately remove any contaminated clothing. Any liquid contaminant on the skin should be soaked up and the affected skin areas cleaned with alkaline soap and warm water. Eye exposures should be treated by rinsing with copious amounts of 4 percent sodium bicarbonate or water. Contact lenses should be removed. Vomiting should not be induced following ingestion exposures, but the mouth should be rinsed. The person should be kept calm and medical attention should be sought as quickly as possible (PAN, 2005; WHO/FAO, n.d.). Medical personnel will treat severe intoxications with a sedative and anticonvulsant (IPCS, 1989). Ingestion of large amounts of deltamethrin should be treated with gastric lavage using a 5 percent bicarbonate solution followed by powdered activated charcoal. Skin irritation may be treated with a soothing agent and exposure to light should be avoided (WHO/FAO, n.d.)

CHRONIC EXPOSURE

NONCANCER ENDPOINTS

Little data are available for humans following chronic exposures to deltamethrin; however, it is not likely to cause long-term problems when used under normal conditions. In humans, suspected chronic effects include choreoathetosis, hypotension, prenatal damage, and shock (EXTOXNET, 1995). Chronic occupational exposure to deltamethrin caused skin and eye irritation; however, no long-term effects were seen (Barlow et al., 2001; EXTOXNET, 1995). After 1 year of using bednets treated with a target does of 25 mg/m^2 deltamethrin, skin irritation occurred one week after treatment, and runny nose and sneezing in the first days of use were reported for target does of 10–30 mg/m^2. No chronic effects were reported (Barlow et al., 2001). Data in animals indicate that oral exposure to deltamethrin is not highly toxic (Barlow et al., 2001; EXTOXNET, 1995; WHO/FAO, n.d.).

In studies of reproductive toxicity in rats, no effects were seen on male or female fertility; number of implantation sites; litter size at birth; or pre- or postnatal survival in rats, mice, and rabbits (Barlow et al., 2001). No effects on reproduction were observed in a 3-generation rat study, but slight embryotoxicity was seen (EXTOXNET, 1995; Barlow et al., 2001). Dose-related decreases in maternal weight gain were seen in pregnant mice dosed with deltamethrin on gestational days 7 to 16. However, no effect on the number of implants, fetal mortality, fetal weight, or malformations was seen (EXTOXNET, 1995). Deltamethrin is not teratogenic in mice, rats, or rabbits at doses that produced clinical signs of toxicity in pregnant dams (Barlow et al., 2001; EXTOXNET, 1995; WHO/FAO, n.d.). Mutagenicity studies in mice, rats, and rabbits indicate that deltamethrin is not mutagenic (Barlow et al., 2001; EXTOXNET, 1995; WHO/FAO, n.d.)

CANCER ENDPOINTS

IARC (1991) has classified deltamethrin as a Group 3 chemical, "not classifiable as to its carcinogenicity in humans." No human carcinogenicity data are available for deltamethrin (IARC, 1991; EXTOXNET, 1995). Long-term dietary studies in rats, mice, and dogs did not find evidence of carcinogenicity (IPCS, 1990). Microbial, mammalian cell, and *in vivo* mammalian mutagenicity studies support the evidence that deltamethrin is not carcinogenic (WHO/FAO, n.d.).

TOXICOKINETICS

Deltamethrin metabolism has not been well studied in humans. It is expected to be similar to metabolism in rodents (Barlow et al., 2001). Deltamethrin is readily absorbed via the gastrointestinal tract, inhalation, and less so through intact skin. The rate at which it is absorbed depends on the carrier or solvent used. Once absorbed, deltamethrin is readily metabolized and excreted (Barlow et al., 2001; IPCS, 1989, 1990; WHO/FAO, n.d). Similar metabolism and excretion patterns have been observed in extensive studies in rats, mice, and cows. Deltamethrin is metabolized in the liver by microsomal esterases and oxidases. It is distributed to the gut wall and liver. The parent compound is cleaved into cyclopropanecarboxylic acid and 3-phenoxybenxyl alcohol, which is then oxidized to 3-phenolbezoic acid. 3-Phenoxybenxoic acid is the major excretion compound. Hydroxylation of this moiety can occur before or after hydrolysis (Barlow et al., 2001; WHO/FAO, n.d.; EXTOXNET, 1995; IPCS, 1990). In rats, approximately 13 to 21 percent of deltamethrin is eliminated unchanged in the urine and feces within 2 to 4 days; however, the metabolites of the cyano substituent are eliminated more slowly. The half-life of deltamethrin in the brains of rats is 1 to 2 days. Levels of the metabolites remain higher, especially in the skin, stomach, and body fat, with a half-life of 5 days in body fat (Barlow et al., 2001; EXTOXNET, 1995). Following oral exposure, deltamethrin is completely eliminated within 6 to 8 days (WHO/FAO, n.d.). In feces, 7 to 15 percent of the oral dose is found as the parent compound and its hydroxylates; the hydrolysis products are mainly excreted in the urine. A smaller amount is found in the skin as thiocyanate (WHO/FAO, n.d.)

ECOLOGICAL EFFECTS

ACUTE EXPOSURE

Toxicity in Non-Targeted Terrestrial Organisms

Deltamethrin, like other pyrethroids, is very unlikely to harm terrestrial organisms other than its targets, such as mosquitoes and other pests (EXTOXNET, 1996). It has a very low toxicity in birds (IPCS, 1990; IPCS, 1989). Oral LD_{50} values range from greater than 1,800 mg/kg in grey partridge to greater than 4,000 mg/kg in ducks (IPCS, 1989). An 8-hour LD_{50} of more than 4,640 mg/kg diet was reported in ducks, and the 8-hour LD_{50} in quail was greater than 10,000 mg/kg diet (EXTOXNET, 1995). As with other pyrethroid insecticides, deltamethrin is extremely toxic to honey bees, with a 24-hour LD_{50} of 0.079 for technical deltamethrin and 0.4 µg ai/bee for the EC formulation. The contact LD_{50} for bees is reported to be 0.05 µg ai/bee. However, in real-life applications, serious effects have not been noticed due to low application rates and lack of environmental persistence. Deltamethrin is also very toxic to *Typhodromum pyri*, a predatory mite; *Encarsia Formosa*, a parasitic wasp; and spiders (EXTOXNET, 1995; IPCS, 1990).

Toxicity in Non-Targeted Aquatic Systems

In the laboratory, deltamethrin is very toxic to fish and aquatic arthropods. However, under normal use conditions in the environment, no deleterious effects have been observed due to its low application rates and lack of persistence (EXTOXNET, 1995; IPCS, 1990). The reported 96-hour LC_{50} value for technical deltamethrin ranges from 0.39 µg/L in rainbow trout to 3.5 µg/L in *Sarotherodon mossambicus*. For the emulsifiable concentrate, LC_{50} values range from 0.59 µg/L in *Salmo salar* (96-hour) to 4.7 µg/L in brown trout (48-hour). For ultra-light volume concentrate, LC_{50} value ranges from 82 µg/L in bleak to 210 µg/L in common carp. In Daphnia, the reported 48-hour LC_{50} for technical deltamethrin is 5 µg/L (IPCS, 1990). Deltamethrin can accumulate in fish. Fathead minnows accumulated deltamethrin without any effect on mortality (EXTOXNET, 1995). Deltamethrin is also highly toxic to aquatic macroinvetebrates such as lobster (IPCS, 1989).

CHRONIC EXPOSURE

Due to low application rates and low persistence of deltamethrin in both terrestrial and aquatic environments, serious adverse effects are not anticipated from chronic exposures (HSDB, 2005)

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PROFILE FOR DIFLUBENZURON

CAS REGISTRY NUMBER 35367-38-5

CHEMICAL SUMMARY

Diflubenzuron (N-[[(4-chlorophenyl)amino] carbonyl]-2,6-difluorobenzamide or 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea) is a benzamide insecticide used to selectively control insects and parasites. Diflubenzuron was first registered in the United States in 1979 for use as an insecticide. EPA issued a Registration Standard for diflubenzuron in September, 1985. A reregistration eleigibility standard was published in 1997 (EPA 1997). A Final Work Plan for a registration review was published in 2013 (EPA 2013a). Recent tolerances have been established for commodities in the Federal Register 40 CFR Part 180 (2014 and 2016).

In the Registration Standard, EPA classified all diflubenzuron end-use products as Restricted Use pesticides due to aquatic invertebrate toxicity. Currently in the US it is registered as an acaricide/insecticide (insect growth regulator) for use on citrus, cotton, mushrooms, pastures, soybeans, ornamentals; for wide-area general outdoor treatment, standing water and sewage system uses; for forest trees; and for cattle. Target pests include many leaf-eating larvae of insects feeding on agricultural, forest and ornamental plants (e.g., gypsy moth, forest tent caterpillar, Nantucket pine tip moth, velvet bean caterpillar, Mexican bean beetle, green cloverworm, beet armyworm, mosquito larvae, aquatic midge, rust mite, bollweevil, citrus root weevil complex, West Indian sugarcane rootstalk borer/weevil, sciarid fly and face fly).

Diflubenzuron toxicity in insects is based upon inhibition of chitin production, and thus interfering with growth of an exoskeketon. Therefore, it has relatively low toxicity to non-insect species compared to organochlorine pesticides. Although EPA has determined that there is no evidence of carcinogenicity for diflubenzuron per se (Group E); p-chloroaniline (PCA), a metabolite of diflubenzuron, is classified as a probable human carcinogen (Group B2), and EPA has also determined that the metabolite p-chlorophenylurea (CPU) has the same carcinogenicity potential as PCA. The effects of diflubenzuron have been studied extensively in mammalian (e.g., rats, mice, rabbits, guinea pigs, dogs) and nonmammalian species (e.g., birds, fish and aquatic/terrestrial invertebrates) (WHO 2006a). In terms of non-insect toxicity, methemoglobinemia and sulfhemoglobinemia are generally employed as sensitive endpoints. Methemoglobinemia results when large quantities of methemoglobin, caused by certain chemicals that convert the ferrous iron in hemoglobin to ferric iron, accumulate in the blood. Methemoglobin may interfere with the oxygen carrying capacity of the blood. Sulfhemoglobinemia results when certain chemicals react with hemoglobin to form sulfhemoglobin, another abnormal form of hemoglobin, which again cannot react normally with oxygen. However, WHO has classified diflubenzuron as "unlikely to present an acute hazard in normal use". Diflubenzuron generally has low acute or chronic toxicity when given by various routes (oral, dermal and inhalation) to non-insect species. There is no evidence of neurotoxicity, fetotoxicity, carcinogenicity, or teratogenicity in mammalian tests (WHO 2006a).

HUMAN HEALTH EFFECTS

DATA QUALITY AND QUANTITY

Diflubenzuron has been studied and reviewed in terms of human toxicity. Key recent regulatory reports include the following:

- EPA 1997. Reregistration Eligibility Decision (RED): Diflubenzuron.
- EPA 2007. Diflubenzuron. Human Health Risk Assessment for the Proposed Establishment of an Emergency Exemption Tolerance for Use in/on Lemons.
- EPA 2013. Diflubenzuron Final Work Plan. Registration Review.

- WHO 2006a. WHO Specifications and Evaluations for Public Health Pesticides: Diflubenzuron.
- WHO 2006b. Report of the Ninth WHOPES Working Group Meeting. Review of Dimilin [diflubenzuron] GR and DT, Vectobac DT, Aqua K-Othrine, Aqua Reslin Super.

Diflubenzuron is also listed in EPA's Human Health Benchmarks for Pesticides database: (https://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home).

TOXICITY

The World Health Organization (WHO) has established an Acceptable Daily Intake (ADIs) for diflubenzuron. The toxicology of diflubenzuron was first evaluated in 1994. In 2002, WHO concluded that the long-term intake of residues of diflubenzuron in food was unlikely to present a public health concern. WHO also concluded that an acute reference dose (RfD) was unnecessary and therefore that short-term intake of diflubenzuron residues is unlikely to present a public health concern. The previously established ADI of 0 to 0.02 mg/kg/d, based upon a no observed adverse effect level (NOAEL) for hematological effects of 2 mg/kg/d in 2-year studies in rats and a 52-week study in dogs, was confirmed in 2002 (WHO 2006a). A safety factor of 100 was applied to result in the ADI.

EPA (https://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home) lists a chronic RfD of 0.02 mg/kg/d (the same as the WHO ADI), and a chronic human health benchmark for pesticides (HHBP) of 140 ppb (in water). The listed supporting document is EPA (2007), but this report provides few details. However, EPA (1997) indicates that the RfD was based upon a NOAEL of 2.0 mg/kg/d in the 52- week chronic oral study in dogs. An uncertainty factor (UF) of 100 was included to account for interspecies extrapolation and intraspecies variability.

Additional benchmarks were derived by EPA in 2014 (EPA 2014). These include a short-term dermal benchmark of 5 mg/kg/d (NOAEL of 500 mg/kg/d from a 21-d rat dermal study, 100 fold UF), an "intermediate" (1 to 6 mo) dermal benchmark of 0.02 mg/kg/d (NOAEL of 2 mg/kg/d from a 13 wk dog oral study, 100 fold UF), an acute inhalation benchmark of 0.2 mg/kg/d (NOAEL of 20.3 mg/kg/d from a 28-d rat inhalation study, 100 fold UF), an "intermediate" inalation benchmark that is the same as the acute benchmark, and a chronic inhalation benchmark of 0.02 mg/kg/d, which is the same as the chronic oral value.

HUMAN TOXICITY BENCHMARK SUMMARY

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Chronic	Oral	0.02	mg/kg/d	RfD based upon NOAEL of 2.0 mg/kg-d, methemoglobinemia in a 52-week oral study in dogs. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations).	EPA 2014, EPA 1997
Chronic	Oral	140	ppb	HHBP, calculated from RfD above	EPA 2014, EPA 1997
Acute	Dermal	5.0	mg/kg/d	NOAEL of 500 mg/kg/d based upon methemoglobinemia in a 21-d dermal study in rats. An UF of 100 was applied by EPA to derive the RfD (10x	EPA 2014

Duration	Route	Benchmark Value	Units	Endpoint	Reference
				interspecies variability, 10x sensitive human subpopulations.)	
Intermediate	Dermal	0.02	mg/kg/d	NOAEL of 2 mg/kg/d based upon methemoglobinemia in a 13-week oral study in dogs. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations.) A 0.5% absorption factor is suggested for application in risk assessment.	EPA 2014
Acute, Intermediate	Inhalation	0.2	mg/kg/d	NOAEL of 20.30 mg/kg/d based upon a 28-d inhalation study in rats. No effect observed at highest tested dose. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations).	EPA 2014
Chronic	Inhalation	0.02	mg/kg/d	NOAEL of 2.0 mg/kg/d based upon methemoglobinemia in a 52-week oral study in dogs. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations).	EPA 2014
Chronic	Oral	0.02	mg/kg/d	NOAEL for hematological effects of 2 mg/kg/d in 2-year studies in rats and a 52-week study in dogs, A safety factor of 100 was applied to result in the ADI	WHO 2006a

Abbreviations: ADI= acceptable daily intake, FQPA= Food Quality Protection Act, HHBP=human health benchmark for pesticides, NOAEL= no observed adverse effect level, RfD= reference dose, UF= uncertainty factor

ECOLOGICAL EFFECTS

DATA QUALITY AND QUANTITY

EPA is currently conducting Biological Evaluations (BEs) for assessing risks to threatened and endangered species from selected pesticides. These BEs generally include many types of terrestrial, aquatic (both

freshwater and marine), and avian animal species; as well as plants. At this time, BEs for diflubenzuron appear to have been focused on threatened/endangered species; specifically the California Red-Legged Frog (EPA 2009) as well as some salmonids (EPA 2013b). In both cases, the primary effect of concern is toxicity to invertebrate prey species, as opposed to the species of concern themselves.

The majority of studies and information are available for aquatic toxicity, as described below.

ENVIRONMENTAL BEHAVIOR

Dibenzuron's use as an insecticide (typically sprays or dusts) will result in its direct release to the environment. If released to the atmosphere, a vapor pressure of 9E-10 mm Hg at 25 deg C indicates diflubenzuron will exist in the particulate phase in the ambient atmosphere. Particulate-phase diflubenzuron will be removed from the atmosphere by wet and dry deposition. Diflubenzuron is susceptible to direct photolysis in sunlight. If released to soil, diflubenzuron is expected to have no mobility based upon K_{oc} values of 6790 to 10600. Volatilization from moist soil surfaces is not expected to be an important fate process based upon an estimated Henry's Law constant of 4.6E-09 atm-m^3/mole. Diflubenzuron is not expected to volatilize from dry soil surfaces based upon its vapor pressure (NLM 2016).

Diflubenzuron has a photodegradation half-life of 11.3 d on soil surfaces exposed to sunlight. Microorganisms are important in the degradation of diflubenzuron from soil. Field dissipation half-lives range from 2 to 35 d, and bare ground dissipation half-lives range from 5.8-13.2 d. If released into water, diflubenzuron is expected to adsorb to suspended solids and sediment based upon the K_{oc} values. Volatilization from water surfaces is not expected to be an important fate process based upon the Henry's Law constant (NLM 2016).

A bluegill sunfish bioconcentration factor (BCF) range of 34-360 has been measured for diflubenzuron. Hydrolysis is not an important fate process at pH 7, where half-lives exceed 180 d at 25 deg C. The hydrolysis half-life is 32.5 d at pH 9. The direct photolysis half-life of diflubenzuron in aqueous solution under natural sunlight is 80 d. Faster photodegradation half-lives have been reported using river water. Biodegradation half-lives averaged between 14 and 32 d in screening tests using marine-sediment and marine-water, respectively, suggesting biodegradation is an important fate process in water (NLM 2016).

TOXICITY

Dibenzuron has been studied and reviewed in terms of aquatic toxicity under the Clean Water Act. The following values are from the EPA Office of Pesticide Programs database (at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/aquatic-life-benchmarks-pesticide-registration).

ECOLOGICAL TOXICITY BENCHMARK SUMMARY

Duration	Species	Value	Units	Endpoint
Acute	Fish	64500	ug/L	Toxicity value x LOC. For acute fish, toxicity value is generally the lowest 96-hour LC50 in a standardized test (usually with rainbow trout, fathead minnow, or bluegill), and the LOC is 0.5.
Chronic	Fish	100	ug/L	Toxicity value x LOC. For chronic fish, toxicity value is usually the lowest NOEAC from a life-cycle or early life stage test (usually with rainbow trout or fathead minnow), and the LOC is 1.

Acute	Invertebrates	0.0014	ug/L	Toxicity value x LOC. For acute invertebrate, toxicity value is usually the lowest 48- or 96-hour EC50 or LC50 in a standardized test (usually with midge, scud, or daphnids), and the LOC is 0.5.
Chronic	Invertebrate	0.00025	ug/L	Toxicity value x LOC. For chronic invertebrates, toxicity value is usually the lowest NOAEC from a life-cycle test with invertebrates (usually with midge, scud, or daphnids), and the LOC is 1.
Acute	Nonvascular Plants	200	ug/L	Toxicity value x LOC. For acute nonvascular plants, toxicity value is usually a short-term (less than 10 d) EC50 (usually with green algae or diatoms), and the LOC is 1.
Acute	Vascular Plants	190	ug/L	Toxicity value x LOC. For acute vascular plants, toxicity value is usually a short-term (less than 10 d) EC50 (usually with duckweed) and the LOC is 1.

Notes:

Values from https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/aquatic-life-benchmarks-pesticide-registration

Abbreviations: EC_{50}= 50% effect concentration, LC_{50}= 50% lethal concentration, LOC=level of concern, NOAEC=no observed adverse effect concentration

The ecological data annex (D-4) contains further information on ecological toxicity values.

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PROFILE FOR ETOFENPROX:

CAS REGISTRY NUMBER 80844-07-1

SUMMARY OF INSECTICIDE

CHEMICAL HISTORY

Etofenprox is a non-ester pyrethroid-like insecticide and acaricide used in agricultural, horticultural, and public health applications. Its toxicity and mode of action (acting on the central nervous system) are similar to other pyrethroids (WHO/FAO, 1993; WHO, 1999; NIH, 2005). For mosquito control, etofenprox is used on bed nets and other materials that are dipped in it to protect the user. WHO has classified etofenprox as low risk for acute toxicity in humans under normal use conditions (WHO, 1999). Typical symptoms of acute exposure are likely to be similar to other pyrethroid insecticides. At high doses, hunched posture, lethargy, body tremors, and respiratory distress were reported in laboratory animals. Etoxfenprox does not inhibit cholinesterase activity. At high doses, long-term exposure can affect organs such as the thyroid and kidneys. Reproductive and developmental effects are not expected. Etofenprox is available as the technical product and formulated wettable powders and emulsifiable concentrates. Etofenprox is classified as Group C, possible human carcinogen.

DESCRIPTION OF DATA QUALITY AND QUANTITY

The available data on etofenprox are limited. Relevant references include the following:

- Pesticide Residues in Food – 1993. Evaluation Part II Toxicology. Etofenprox (WHO/FAO, 1993)
- Etofenprox Evaluation (FAO, 1993)
- Summary of Toxicology Data: Etofenprox (CalEPA, 2003)

SUMMARY TABLE

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute, Intermediate, Chronic	Inhalation	0.1	mg/kg/day	NOAEL for systemic effects in rats with UF of 100 applied	NYSDEC (2005)
Acute, Intermediate, Chronic	Oral	0.037	mg/kg/day	Proposed chronic RfD based NOEL in rats with UF of 100 applied	NYSDEC (2005)
Acute, Intermediate	Dermal	0.4	mg/kg/day	LOAEL (skin lesions) in rats with UF of 1,000 applied	NYSDEC (2005)
Chronic	Dermal	0.037	mg/kg/day	Adopt chronic oral RfD; assume no first pass effects and 100% absorption	NYSDEC (2005)
Cancer	Inhalation, Oral, Dermal	0.0051	per mg/kg/day	CSF for thyroid adenomas and carcinomas in rats	NYSDEC (2005)

For inhalation exposure, a NOEL of 0.04 mg/L (equivalent to 10.6 mg/kg/day) was identified for hematological and systemic effects in rats (study citation not provided) exposed to etofenprox for 90 days

(NYSDEC, 2005). An uncertainty factor of 100 was applied to account for intrahuman and interspecies variation. This value is appropriate for all exposure durations.

For oral exposure, EPA calculated a chronic RfD of 0.037 mg/kg/day based on a NOEL in a chronic rat feeding study (study citation not provided). An uncertainty factor of 100 was applied. EPA's Integrated Risk Information System (IRIS) has not yet adopted this value (NYSDEC, 2005). This value is appropriate for all exposure durations.

For dermal exposure, a LOAEL of 400 mg/kg/day for skin lesions was reported (study citation not provided) in a 28-day dermal study in rats (no systemic effects were observed). An uncertainty factor of 1,000 was applied to account for the use of a LOAEL and intrahuman and interspecies variation (NYSDEC, 2005). This value is appropriate for short- and intermediate-term exposures. For long-term exposures, the chronic oral RfD was adopted for dermal exposures.

EPA has classified etofenprox as Group C, possible human carcinogen. To assess potential carcinogenic risks, EPA derived a cancer slope factor (CSF) of 5.1 x 10^{-3} per mg/kg/day based on increased thyroid follicular cell adenomas and carcinomas in a two-year rat feeding study (NYSDEC, 2005).

INSECTICIDE BACKGROUND

CASRN:	80844-07-1
Synonyms:	Ethofenprox. Ethophenprox, Ephofenprox, 1-((2-(4-Ethoxyphenyl)-2-methylpropoxy)methyl)-3-phenoxy benzene, 3-Phenoxybenzyl 2-(4-ethoxyphenyl)-2-methylpropyl ether, MTI 500, BRN, 707478121 percentEtofenprox aerosol , 1 percentEtofenprox Fogger, 2-(4-Ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether , Benzene, 1-((2-(4-ethoxyphenyl)-2-methylpropoxy)methyl)-3-phenoxy- , Benzene, 1-((2-(4-ethoxyphenyl)-2-methylpropoxy)methyl)-3-phenoxy- (9CI) RF 316 , SAN 811 I (NIH, 2005; FAO, 1993; PAN, 2005)
Chemical Group:	non-ester pyrethroid (Hemingway, 1995)
Registered Trade Names:	Carancho 2.5 EC, Polido 2.5 EC, Trebon 10 EC, Trebon 10 EW, Trefic 20 WP, Vectron 10 EW, Vectron 20 WP, Zoecon RF-316 (WHO, 2002; FAO, 1993; PAN, 2005)

USAGE

Etofenprox is used as a broad spectrum insecticide to combat a wide variety of pests on an assortment of crops including rice, fruits, vegetables, corn, soybeans, and tea. Etofenprox is effective against Lepidoptera, Hemiptera, Coleoptera, Diptera, Thysanoptera, and Hymenoptera at low rates. Because of its pyrethroid-like activity, it is active against insects that are resistant to carbamate or organophosphorus insecticides, including strains of rice green leafhopper and planthoppers (WHO/FAO, 1993; FAO, 1993). Etofenprox is also used in public health applications, including mosquito control, and on livestock (WHO/FAO, 1993; Hemingway, 1995). Etofenprox is a WHO Pesticide Evaluation Scheme (WHOPES)-recommended insecticide for the indoor spraying of malaria vectors. Application of 0.1 to 0.3 mg/m^2 is effective for 3 to 6 months (WHO, 2003). Technical grade etofenprox (97 percent etofenprox) is labeled for use in pesticide formulations for use in residential, commercial, and industrial uses. Etofenprox aerosol (1 percent) is labeled to kill cockroaches, ants, fleas, ticks, spiders, and other listed insects in residential, commercial, and industrial applications (NYSDEC, 2005). Etofenprox is not a restricted use chemical (PAN, 2005).

FORMULATIONS AND CONCENTRATIONS

Etofenprox is available in technical grade, emulsifiable concentrates, and wettable powder formulations (WHO, 1999; FAO, 1993). Technical grade etofenprox is typically 96.3 percent etofenprox with < 1 percent impurities (FAO, 1993). It may be mixed with carriers or solvents resulting in the commercial formulations. The most common formulations are a 20 percent wettable powder and a 20 percent emulsifiable concentrate. These may be used on all crops; however 10 percent or 30 percent formulations are used in some countries (FAO, 1993). WHO indicated that the content of etofenprox in the formulated products must be declared and shall not exceed the listed standards. Technical grade etofenprox must have no less than 985 g/kg etofenprox. The wettable powder should contain > 25–100 g/kg +/- 10% of the declared content, 100–250 g/kg +/- 6% of the declared content, or > 250–500 g/kg +/- 5% of the declared content (WHO, 1999). For mosquito netting treatment, etofenprox is a WHOPES-recommended insecticide at doses of 200 mg ai/m^2 of netting of a 10 percent EW formulation. The amount of etofenprox that is recommended for treatment of mosquito netting is 30 ml of a 10 percent EW formulation (WHO, 2003).

SHELF LIFE

Etofenprox is stable to temperatures up to 80°C for up to 3 months. At 100°C, it degrades partially. A half-life of 4 days was calculated for radiolabeled etofenprox exposed to high intensity heat lamps (FAO, 1993).

DEGRADATION PRODUCTS

In soil, etofenprox is broken down by oxidation. The main degradation products are 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzoate and 2-(4-ethoxyphenyl)-2-methylpropyl 3-hydroxybenzyl ether. It is metabolized by desethylation of the ethoxyphenyl group, hydroxylation of the phenoxy ring, and oxidation of the benzyl moiety followed by cleavage of the ether linkage to form polar compounds. In animals, conjugates are formed (FAO, 1993).

ENVIRONMENTAL BEHAVIOR

FATE AND TRANSPORT IN TERRESTRIAL SYSTEMS

Studies of adsorption and leaching of etofenprox in Yamanashi sandy loam (78 percent sand, 11 percent silt, 11 percent clay), Chiba light clay (28 percent sand, 39 percent silt, 32 percent clay), and Shizuoka light clay (43 percent sand, 26 percent silt, 31 percent clay) revealed low translocation. Unchanged etofenprox was not found in deeper layers of the soil when it was applied just before application of glass columns. When radiolabeled soil was preincubated, the majority or the radioactivity remained in the top 5 cm of soil. Unchanged etofenprox was not found in the elutes (FAO, 1993).

Under laboratory conditions the half-life of etofenprox in soil is 6 to 9 days, with only minor differences between Yamanashi sandy soil, Chiba light clay soil, and Shizuoka light clay soil. Etofenprox content decreased 15 percent over 3 weeks. Degradation occurred by oxidation to 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzoate and 2-(4-ethoxyphenyl)-2-methylpropyl 3-hydroxybenzyl ether. In nonsterile soil, 80 percent of the applied etofenprox was decomposed within two weeks; no degradation occurred in sterile soil (FAO, 1993).

In field studies, the half-life of etofenprox was approximately 79 days in loam soil (8.2 percent clay, 7.5 percent organic carbon), 62 days in clayish loam soil (21 percent clay, 2.4 percent organic carbon), 39 days in volcanic ash loam (10 percent clay, 6.2 percent organic carbon), and 9 days in alluvial clayish loam (2 percent clay, 2.8 percent organic carbon) (FAO, 1993).

Photodegradation may be an important fate process for etofenprox on plant surfaces. Similar degradation pathways have been shown in laboratory studies of photodegradation from glass disc surfaces and in studies on bean leaves (FAO, 1993).

FATE AND TRANSPORT IN AQUATIC SYSTEMS

Under laboratory conditions, etofenprox is stable in aqueous solutions of 1N NaOH or 1N HCl for a period equal to or greater than 10 days (FAO, 1993). It is stable in neutral and acidic environments at 25°C and in darkness, with an estimated half-life of greater than 1 year. However, a more rapid breakdown is seen under real life conditions. In city water treated with 200 g/L etofenprox, 70 percent degradation was observed after 1 week and 93 percent after 3 weeks. The rapid degradation was attributed to the presence of sunlight.

HUMAN HEALTH EFFECTS

ACUTE EXPOSURE

Effects/Symptoms

There are limited data on the acute toxicity of etofenprox in humans. Because its toxicity and mode of action are similar to other pyrethroids, the general symptoms of pyrethroid exposure are expected to occur following acute etofenprox exposure. Technical grade etofenprox is not expected to present an acute hazard to humans under normal use conditions (WHO, 2005; WHO/FAO, 1993).

In mice, rats, and dogs, etofenprox and 1 percent Etofenprox Aerosol have low acute toxicity by oral, dermal, and inhalation routes of exposure (WHO/FAO, 1993, PAN, 2005, NYSDEC, 2005). Reported LD_{50} values for mice exposed to etofenprox (96 percent) were >107.2 for oral exposures and >2.14 g/kg for dermal (24-hour) exposures. In rats, an oral LD_{50} of >42.88 g/kg, a dermal 24-hour LD_{50} of 2.14 g/kg bw, and an inhalation LC_{50} of > 5.9 g/m^3 were reported. The oral LD_{50} in dogs was reported as >5.0 g/kg. The oral LD_{50} of Trebon 20 EC (20 percent etofenprox emulsifiable concentrate) is reported as >5 g/kg in both mice and rats, and the dermal LD_{50} is reported as > 2 g/kg in rats (WHO/FAO, 1993).

Acute oral studies of high-dose exposure to etofenprox showed central nervous system effects in both mice and rats. Dose-related decreases in spontaneous motor activity were observed in mice at high doses. In rats, a dose-related effect on EEG of the frontal lobe was seen at a similarly high dose. In rabbits, a 1 percent etofenprox formulation did not produce much skin or eye irritation. However, technical etofenprox is moderately irritating to the skin but not the eyes. No dermal sensitization was observed in tests on guinea pigs (NYSDEC, 2005; WHO/FAO, 1993). In subchronic (13-week) dietary studies in mice and rats, growth retardation and increased liver weights were observed at lower doses and hunched posture, lethargy, body tremors, and respiratory distress were reported at the highest dose tested (WHO/FAO, 1993).

Treatment

Etofenprox's toxicity and mode of action are similar to other pyrethroids. No chemical-specific data were located on the treatment of etofenprox exposure; however, generalized treatment for pyrethroids should be appropriate. Treatment of etofenprox exposure depends on the symptoms of the exposed person. If a person exhibits signs of typical pyrethroid toxicity following etofenprox exposure (nausea, vomiting, shortness of breath, tremors, hypersensitivity, weakness, burning, or itching), they should immediately remove any contaminated clothing. Any liquid contaminant on the skin should be soaked up and the affected skin areas cleaned with alkaline soap and warm water. Eye exposures should be treated by rinsing with copious amounts of 4 percent sodium bicarbonate or water. Contact lenses should be removed. Vomiting should not be induced following ingestion exposures, but the mouth should be rinsed. The person should be kept calm and medical attention should be sought as quickly as possible. Medical personnel will treat severe intoxications with a sedative and anticonvulsant. Ingestion of large amounts of etofenprox should be treated

with gastric lavage using a 5 percent bicarbonate solution followed by powdered activated charcoal. Skin irritation may be treated with a soothing agent and exposure to light should be avoided (WHO, 1999)

CHRONIC EXPOSURE

NONCANCER ENDPOINTS

Little data are available for humans following chronic exposures to etofenprox. No compound-related effects were reported in workers occupationally exposure to unspecified concentrations of technical etofenprox for 1.5 to 5.5 years. Blood pressure measurements, X-rays, hematology measurements, blood chemistry analysis, urinalysis, and EKGs were taken and interviews conducted (WHO/FAO, 1993).

In chronic animal studies, rodents appear to be the most sensitive species (WHO/FAO, 1993). Following long-term oral exposure, systemic organ toxicity has been observed, including effects on the thyroid, kidneys, and liver in rats, mice, and dogs (NYSDEC, 2005; CalEPA, 2003; WHO/FAO, 1993). A 90-day inhalation exposure of rats resulted in increased heart, lung, liver, and kidney weights (NYSDEC, 2005). Etofenprox is not a cholinesterase inhibitor (PAN, 2005).

Etofenprox exposure does not produce significant reproductive or developmental toxicity in animals (NYSDEC, 2005; CalEPA, 2003). No adverse effects on reproductive parameters were seen in a two-generation feeding study or in segment I and II gavage study where rats were exposed to high levels in the diet and by gavage, respectively (CalEPA, 2003; WHO/FAO, 1993; NYDEC, 2005). No significant developmental toxicity in the absence of maternal toxicity has been reported following etofenprox exposure in animals (NYSDEC, 2005; CalEPA, 2003). Some developmental effects (increased incidence of malformations and visceral abnormalities) have been reported in rat offspring; however, they only occurred at doses that also caused maternal toxicity (WHO/FAO, 1993). Reduced fetal body weight and increased postimplantation loss were observed in rabbits at maternally toxic levels (NYSDEC, 2005).

Etofenprox is not mutagenic. Results from genotoxicity studies in bacteria, mammalian cells, *in vitro*, and *in vivo* in mice were all negative (WHO/FAO, 1993; CalEPA, 2003).

CANCER ENDPOINTS

EPA has classified etofenprox as Category C, possible human carcinogen, and calculated a cancer potency slope factor of 5.1×10^{-3} per mg/kg/day (NYSDEC, 2005). The available animal data show evidence of carcinogenicity in the absence of any human data (PAN, 2005). An increased incidence of thyroid follicular cell adenomas was seen in a two-year rat feeding study (WHO/FAO, 1993; CalEPA, 2003; NYSDEC, 2005).

TOXICOKINETICS

Etofenprox is readily absorbed from the gastrointestinal tract of rats given oral doses. Absorption ranged from 48–93 percent; absorption is dose dependent (WHO/FAO, 1993; FAO, 1993). Dermal absorption studies in male rats revealed that more than 90 percent of the total dose of 5, 59, or 184 g/cm^2 was recovered up to 96-hours after applications of ^{14}C-labeled etofenprox. Most of the radioactivity was recovered in the skin wash prior to sacrifice. The absorbed radioactivity was less than 7 percent after 96 hours (CalEPA, 2003). Etofenprox is distributed to fat as the parent compound, where the highest tissue concentrations are observed. Following oral administration, it is rapidly excreted, mainly in feces. Within 5 days, 85 to 90 percent was excreted in the feces, with lesser amounts (3 to 4 percent) in the urine. Only 3 to 4 percent remained in the body after 5 days. Etofenprox is not excreted in bile. It is excreted unchanged in the milk of dairy cows fed diets containing etofenprox. In rats, biotransformation mainly involves desethylation of the ethoxyphenyl group, hydroxylation of the phenoxy ring and oxidation of the benzyl methylene group. Although

gastrointestinal absorption occured at a slower rate in dogs than rats, the major routes of biotransformation were the same (WHO/FAO, 1993; FAO, 1993; CalEPA, 2003).

ECOLOGICAL EFFECTS

ACUTE EXPOSURE

Toxicity in Non-Targeted Terrestrial Organisms

No data are available on the toxicity of etofenprox in birds or other non-target terrestrial organisms.

Toxicity in Non-Targeted Aquatic Systems

Etofenprox is toxic to aquatic organisms (WHO, 1999). In fish, etofenprox is slightly to moderately toxic. Slight toxicity is supported by the reported average LC_{50} of 49,000 µg/L in Japanese eel, while moderate toxicity is supported by the reported average LC_{50} of 1,845 µg/L in Mozambique tilapia. In addition to mortality, behavioral, biochemical, and physiological changes have been reported in fish exposed to etofenprox . Behavioral changes were reported in Mozambique tilapia exposed to 1,305 µg/L of the etofenprox formulation Trebon. Biochemical changes were seen in carp exposed to 600 µg/L of a 30 percent emulsifiable concentrate of Trebon for 24 hours, and effects were seen at a mean exposure of 300 µg/L for 15 days. Hematological effects and oxygen consumption changes were seen in Mozambique tilapia at concentrations of 1,400 µg/L of 96.3 percent etofenprox (PAN, 2005)

CHRONIC EXPOSURE

Due to low application rates and low persistence of permethrin in both terrestrial and aquatic environments, serious adverse effects are not anticipated from chronic exposures (HSDB, 2005). No specific chronic data are available.

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PROFILE FOR FENITROTHION:

CAS REGISTRY NUMBER 122-14-5

SUMMARY

CHEMICAL HISTORY

Fenitrothion is a general use organophosphate insecticide that is nonsystemic and nonpersistent. It is mostly used in the control of chewing and sucking insects on a wide variety of agricultural crops and in forests, as well as for public health purposes. It is also used as a residual contact spray against mosquitoes, flies, and cockroaches. Fenitrothion is used residentially to control household and nuisance insects (EXTOXNET, 1995; WHO, 2003). Fenitrothion was introduced in 1959 as a less toxic alternative to parathion, with which it shares similar insecticidal properties. Fenitrothion is used heavily in countries that have banned parathion (EXTOXNET, 1995). In the United States, the use of fenitrothion for mosquito control was voluntarily cancelled by the manufacturer in 1995 (U.S. EPA, 1995) and the only registered use is for containerized ant and roach baits (U.S. EPA, 2000b).

The primary route of occupational exposure to fenitrothion is dermal, although inhalation exposures are also possible (U.S. EPA, 1995). Exposure to fenitrothion can cause overstimulation of the nervous system due to cholinesterase inhibition. This may result in nausea, dizziness, confusion, and respiratory paralysis and death at very high exposures (U.S. EPA, 2000b).

DESCRIPTION OF DATA QUALITY AND QUANTITY

EPA has developed quantitative human health benchmarks (acute and chronic oral RfDs and inhalation and dermal benchmarks) for fenitrothion. Relevant review data resources include the following

- Reregistration Eligibility Decision (RED) Fenitrothion (U.S. EPA, 1995)
- Pesticide Information Profiles (PIP) for Fenitrothion (EXTOXNET, 1995)
- Specifications for Pesticides Used in Public Health: Fenitrothion (WHO, 1999)
- Pesticide Residues in Food 2000: Fenitrothion (IPCS, 2000).

SUMMARY TABLE

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute, Intermediate, Chronic	Inhalation	0.0004	mg/kg/day	Inhalation NOAEL of 0.2 µg/L (0.2 mg/kg/day) for neurological effects in rats with UF of 100 applied and adjusted for intermittent exposure	U.S. EPA (1999a)
Acute	Oral	0.13	mg/kg/day	Acute oral RfD based on neurological effects in rats	U.S. EPA (1999a)
Intermediate	Oral	0.0013	mg/kg/day	Adopt chronic RfD for intermediate duration	U.S. EPA (1999a)
Chronic	Oral	0.0013	mg/kg/day	Chronic oral RfD for based on NOEL	U.S. EPA

Duration	Route	Benchmark Value	Units	Endpoint	Reference
				for systemic and neurological effects in dogs	(1999a)
Acute, Intermediate, Chronic	Dermal	0.01	mg/kg/day	Dermal LOAEL of 3 mg/kg/day for dermal effects in rabbits	U.S. EPA (1999a)

For inhalation exposure, a NOAEL of 0.2 µg/L (0.2 mg/kg/day)[3] was identified in rats (Coombs et al., 1988) exposed to fenitrothion via inhalation for 6 hours per day, 5 days per week, for 90 days (U.S. EPA, 1999a; IPCS, 2000). The concentration was adjusted for intermittent exposure[4] (0.04 mg/kg/day) and an uncertainty factor of 100 was applied to account for interspecies and intrahuman variation, for an inhalation benchmark of 0.0004 mg/kg/day. This value is appropriate for all exposure durations.

For oral exposure, an acute oral RfD was estimated at 0.13 mg/kg/day based on a NOAEL of 12.5 mg/kg/day for acute neurotoxicity in rats (Beyrouty et al, 1992). An uncertainty factor of 100 was applied to account for interspecies and intrahuman variability (U.S. EPA, 1999a). A chronic oral RfD of 0.0013 mg/kg/day was developed by EPA (1995, 1999a) based on a NOAEL of 0.125 mg/kg/day for systemic effects and plasma acetylcholinesterase inhibition in a long-term feeding study in dogs (Spicer, 1986). An uncertainty factor of 100 was applied to account for interspecies and intrahuman variability (U.S. EPA, 1995, 1999a). The chronic RfD was adopted to represent intermediate-term exposures.

For dermal exposure, a LOAEL of 3 mg/kg/day for dermal irritation and desquamation of the epidermis was identified from 21-day dermal rabbit study (Suetake, 1991); no neurological effects were observed at this concentration (U.S. EPA, 1995). An uncertainty factor of 300 was applied to account for interspecies and intrahuman variability and the use of a less serious LOAEL, resulting in a dermal benchmark of 0.01 mg/kg/day. This value is appropriate for all exposure durations.

INSECTICIDE BACKGROUND

CAS#	122-14-5
Synonyms:	O,O-dimethyl O-(4-nitro-m-tolyl) phosphorothioate (U.S. EPA, 1995) methylnitrophos (Eastern Europe) (EXTOXNET, 1995)
Chemical Group:	Organophosphate (EXTOXNET, 1995; U.S. EPA, 2000a)
Registered Trade Names:	Accothion, Agrothion, Bay 41831, Bayer 41831, Bayer S 5660, Cyfen, Cytel, Dicofen, Dybar, Fenitox, Fenstan, Folithion, Kaleit, Mep, Metathion, Micromite, Novathion, Nuvanol, Pestroy, Sumanone, Sumithion, and Verthion (U.S. EPA, 1995; EXTOXNET, 1995)

[3] Conversion between mg/m^3 and mg/kg/day assumes, for female Wistar rats, an average body weight of 0.156 kg and inhalation rate of 0.17 m^3/day (U.S. EPA, 1988).

[4] Adjustment for intermittent exposure is the product of air concentration and exposure of 6/24 hours/day and 5/7 days/week.

USAGE

Fenitrothion is a broad spectrum organophosphate insecticide and acaricide (IPCS, 2000) most commonly used in agriculture to control chewing and sucking insects on crops such as rice, cereals, fruits, vegetables, stored grains, and cotton. It is also used in forested areas and to control flies, mosquitoes, and cockroaches, and in public health programs (WHO, 2004). In the United States, fenitrothion is only registered for use as a containerized ant and roach bait. In Australia, it is used on stored wheat (U.S. EPA, 2000b).

FORMULATIONS AND CONCENTRATIONS

There are several formulations for fenitrothion, each containing varying amounts of the active ingredient. The typical formulations for fenitrothion are dusts (2 percent , 2.5 percent, 3 percent, or 5 percent), emulsifiable concentrate (50 percent), flowable, fogging concentrate (95 percent), and wettable powder (40 or 50 percent). It is also available in granules and ultra-low-volume, oil-based liquid spray (EXTOXNET, 1995). Registered formulation types include 0.01563 percent and 1 percent pellets and granular baits. Emulsifiable concentrates are not registered in the Unites States (U.S. EPA, 2000b). The fenitrothion content for various formulations should be declared as follows: technical grade fenitrothion (no les than 910 g/kg), fenitrothion emulsifiable concentrate and wettable powder (above 250 up to 500 g/kg + 5% of declared content, above 500 g/kg + 25 g/kg) (WHO, 1999).

SHELF-LIFE

Like many insecticides, fenitrothion should be stored in a locked, well-ventilated facility, preferably one designated only for insecticide storage. It should not be exposed to sunlight and should be stored away from animal feed and foodstuffs (IPCS, 1991).

Fenitrothion is stable for up to two years if stored between 20 and 25°C; storage temperatures should not exceed 40°C. Fenitrothion is unstable when heated above 100°C and may undergo Pishchemuka isomerization and decompose explosively. Decomposition of fenitrothion is promoted by iron. Therefore, fenitrothion should be stored in enamel, aluminum, or glass containers. Fenitrothion is not stable in alkaline environments (EXTOXNET, 1995). Residues of fenitrothion are stable for up to 147 days in wheat and 174 days in wheat gluten when frozen (-18°C) (U.S. EPA, 1995).

DEGRADATION PRODUCTS

In water, fenitrothion is degraded through photolysis and hydrolysis, with degradation accelerated in the presence of microflora. In soil, fenitrothion is primarily broken down by biodegradation with photolysis also playing a role (WHO, 2003, 2004). Carbon monoxide is the major degradate for aerobic soil metabolism and photolysis. The major nonvolatile degradates for aerobic soil metabolism, anaerobic aquatic metabolism, and photolysis include 3-methyl-4-nitro-phenol (approximately 1 to 22 percent of applied); aminofenitrothion (approximately 13 percent of applied); acetyl-aminofenitrothion (approximately 13 percent of applied); formylaminofenitrothion (4.9 percent of applied); o,o-dimethyl o-(3-carboxy-4-nitrophenyl)phosphorothionte (12.4 percent of applied); fenitrooxon (≤ 4.3 percent of applied); demethylate fenitrothion (approximately 1 percent of applied); and desmethylfenitrooxon (≤ 4.3 percent of applied). Other degradates are present at concentrations less than or equal to 2 percent and include o,o-dimethyl o-(3-methyl-4-nitrophenyl)phosphorothioate-3-methyl-4-nitrophenol; o-methyl (5-methyl o-(3-methyl-4-nitrophenyl)phen-phorothioate; o-methyl o-hydrogen o-(3-methyl-4-nitro-phenyl)phosphate; o,o-dimethyl o-(3-carboxy-4-nitrophenyl)phosphate; 5-methylfenitrothion; and carboxyfenitrooxon. The major degradates in pH 5 and pH 9 solutions are demethylated fenitrothion (10.3 percent of applied) and 3-methyl-4-nitrophenol (1.7 percent of applied). In pH 9 solution, the major degradate is 3-methyl-4-nitrophenol (15.1 percent of the applied),

while demethylated fenitrothion accounts for up to 5.6 percent of applied. The major degradate from hydrolysis in pH 5 and pH 7 buffered solutions is demethylated fenitrothion. The major degradate in pH 9 buffered solution is 3-methyl-4-nitrophenol. Seven degradates were identified from photodegradation in soil. In loam soil, the major nonvolatile degradates from aerobic soil metabolism was 3-methyl-4-nitrophenol. Additional degradates included fenitrooxon, desmethylfenitrooxon, and 3-methyl-4-nitroanisole. The major volatile degradate was carbon monoxide (U.S. EPA, 1995).

ENVIRONMENTAL BEHAVIOR

FATE AND TRANSPORT IN TERRESTRIAL SYSTEMS

In most soil types, fenitrothion degrades rapidly with a half-life ranging from 3 to 25 days (U.S. EPA, 1995). Fenitrothion is mostly found in the top six inches of soil and is not very mobile and only slightly persistent in soil (U.S. EPA, 1995). In nonsterile muck and sandy loam soils, a half-life of less than one week is reported. Fenitrothion is intermediately mobile in soils ranging from sandy loam to clay (EXTOXNET, 1995). However, when applied to silty clay loam, silty clay, and sandy loam under laboratory conditions, fenitrothion appears to be immobile (U.S. EPA, 1995). Fenitrothion leaches very slowly into groundwater from most soils; however, some runoff can occur (WHO, 2004).

FATE AND TRANSPORT IN AQUATIC SYSTEMS

On lakes, surface foam can trap fenitrothion from aerial spraying (EXTOXNET, 1995). In water, fenitrothion is unstable in the presence of sunlight or microbial contamination (WHO, 2003). Laboratory studies at 23°C and pH 7.5 in the dark resulted in a half-life of 21.6 days for buffered lake water and 49.5 days for natural lake water. However, in field experiments, the half-life was 1.5-2 days at pH 7.0-7.5 and 19-23°C (EXTOXNET, 1995). Phenyl labeled [^{14}C]-fenitrothion had a half-life of 4-7 days, while the anaerobic aquatic half-life is reported at 0.82 days. In fish, fenitrothion accumulates rapidly but at low concentrations (U.S. EPA, 1995).

HUMAN HEALTH EFFECTS

ACUTE EXPOSURE

Effects / Symptoms

Acute oral and dermal experimental data are available for human exposures to fenitrothion. No effect on acetylcholinesterase activity was observed in volunteers following a single oral dose of up to 0.33 mg/kg body weight or repeated doses of up to 0.36 mg/kg body weight/day for 4 days. Volunteers ingested technical-grade fenitrothion via capsule at doses of 0.18 mg/kg/day followed 2 weeks to 5 months later by 0.36 mg/kg/day, with each daily dose continued for 4 consecutive treatments. No significant effect of treatment was seen on blood pressure or pulse, and observed clinical signs were not considered to be treatment related. Transient decreases in erythrocyte cholinesterase activity were observed in two volunteers, but no treatment-related changes in hematological or clinical chemistry parameters were observed. No dermal irritation and no effects on cholinesterase activity were observed in volunteers exposed to up to 0.5 mg/kg/day fenitrothion orally followed by 0.1 mg/kg/day dermally to the arms and face for 9 days (IPCS, 2000).

Case reports of humans accidentally or intentionally ingesting fenitrothion indicate that fenitrothion is lethal at oral doses of 3 g. Additionally, death from respiratory insufficiency was observed 6 days after a man ingested 60 mL of a 50 percent emulsion in a suicide attempt. Other acute oral effects included paralysis at 1.5 to 6 g. In patients exhibiting paralysis, plasma cholinesterase was inhibited by 40 percent to more than 80 percent. In patients who consumed 50 to 100 mL of a 50 percent fenitrothion solution either accidentally or in suicide attempts, 6 of 16 died within 5 to 22 days, despite receiving medical attention. Intermediate

syndrome, characterized by muscular weakness affecting the neck, proximal limb, and respiratory muscles, was observed in 7 of 10 survivors. Of those with intermediate syndrome, plasma cholinesterase activity was not observed at time of hospitalization. Recovery ranged from 5 weeks to more than10 weeks in patients with intermediate syndrome, versus 2 to 4 weeks in those without (IPCS, 2000).

No clinical signs were observed in spray operators or villagers one week after exposure to a 5 percent fenitrothion spray. However, a 40–60 percent decrease in cholinesterase activity was observed in spray operators using fenitrothion indoors for 4 weeks in the absence of clinical symptoms of organophosphate toxicity. Orchard spray operators who inhaled a mean concentration of 0.011 µg/L fenitrothion for 3 consecutive days also showed no clinical signs but had lower maximum plasma concentration of fenitrothion than unexposed operators, with relatively rapid clearance from plasma (IPCS, 2000).

In animals, the acute toxicity of fenitrothion is low. The oral LD_{50} ranges from 240 to 1,700 mg/kg in rats, 715 to 1,400 mg/kg in mice, and 500 mg/kg in guinea pigs (EXTOXNET, 1995; IPCS, 2000). The acute dermal LD_{50} is reported to be 890–5,000 mg/kg in rats and greater than 3,000 mg/kg in mice (EXTOXNET, 1995; IPCS 2000). The acute inhalation LC_{50} ranges from 2.2 to 5.0 mg/L in rats (EXTOXNET, 1995; IPCS 2000). In cats, acute oral toxicity was 142 mg/kg (IPCS, 2000). Toxicity is dependent on sex and vehicle used; males are sensitive than females (IPCS, 2000). This is illustrated by the reported acute toxicity of the fenitrothion preparation Sumithion Technical (97.2 percent); the oral LD_{50} is 330 mg/kg in males and 800 mg/kg in females, and the dermal LD_{50} is 890 mg/kg in males and 1,200 mg/kg in females (U.S. EPA, 1995).

The signs of acute fenitrothion toxicity in animals are consistent with cholinesterase inhibition (IPCS, 2000). In hens, no evidence of delayed neurotoxicity or increased neurological lesions was seen following a single dose (WHO, 2004) or acute administration of Sumithion Technical (97.2 percent) (U.S. EPA, 1995). However, the fenitrothion product Sumithion 50EC has been shown to cause delayed neurotoxicity in adult rats as well as humans (EXTOXNET, 1995). In rats, cholinergic signs and erythrocyte and brain cholinesterase inhibition were seen at a number of doses, but cholinergic signs were seen only when brain cholinesterase was inhibited by more than 58 percent or erythrocyte acetyl cholinesterase was inhibited by more than 38 percent (WHO, 2004).

Technical grade fenitrothion (95 percent) does not cause dermal or ocular irritation in rabbits or dermal sensitization in guinea pigs (IPCS, 2000; U.S. EPA, 1995). However, mild dermal irritation was seen following exposure to Sumithion 8-E (77 percent ai) (U.S. EPA, 1995). Other acute effects in animals include those caused by O,O,S-trimethyl phosphorothioate, one of the contaminants of fenitrothion, including cytotoxic effects in rat lungs and modulated immune response in mice (EXTOXNET, 1995).

Treatment

Dermal exposure to fenitrothion should be treated by removing contaminated clothing, rinsing the skin with water, washing the exposed areas with soap and water, then seeking medical attention. If fenitrothion gets into the eyes, they should be rinsed with water for several minutes. Contact lenses should be removed if possible and medical attention should be sought. Ingestion of fenitrothion should be treated by rinsing the mouth and inducing vomiting if the person is conscious. Inhalation exposures require removal to fresh air and rest in a half-upright position. Artificial respiration should be administered if indicated and medical attention should be sought (PAN, 2005).

CHRONIC EXPOSURE

NONCANCER ENDPOINTS

Limited data are available on the chronic toxicity of fenitrothion in humans. Chronic symptoms of toxicity in humans include general malaise, fatigue, headache, loss of memory and ability to concentrate, anorexia,

nausea, thirst, loss of weight, cramps, muscular weakness, and tremors. At sufficient exposure levels, typical symptoms of cholinergic poisoning may be seen (EXTOXNET, 1995). Mild clinical signs such as nausea and dizziness and whole-blood cholinesterase inhibition were observed in spray operators following occupational exposure to fenitrothion used during a 30-day malaria control operation. However, no treatment-related effects were seen in operators spraying fenitrothion for 5 hours/day, 5 days a week, intermittently for 2 years (IPCS, 2000).

The main toxicological finding from long-term animal studies was cholinesterase activity inhibition (red blood cell, plasma, and brain) in all species studied (IPCS, 2000; U.S. EPA, 1995; EXTOXNET, 1995). Signs of poisoning and cholinergic stimulation were also reported at higher levels.

In animals, reproductive and developmental toxicity are of concern. Developmental effects were seen at doses that were maternally toxic in rats. Reduced body weight, viability, and lactation indices were seen in offspring. In rats and rabbits, no fetal toxicity or treatment-induced malformations were seen at the highest dose tested in the presence of maternal cholinergic signs and decreased body weight gain (WHO, 2004). Others have reported an increase in fetal and skeletal variations at doses causing maternal toxicity (U.S. EPA, 1998). Behavioral effects were observed in rat pups following maternal exposure to Sumithion 50EC on gestation days 7 to 15 and included differences in simple behavioral measures and complex measures, which persisted up to 104 days after birth. No effects were seen at lower levels (EXTOXNET, 1995).

Fenitrothion is not teratogenic, mutagenic, or genotoxic in chronically exposed animals and is not expected to cause those effects in humans (EXTOXNET, 1995). Additionally, fenitrothion did not induce immunotoxicity (WHO, 2004).

CANCER ENDPOINTS

Data on the carcinogenic potential of fenitrothion indicate that it is unlikely to pose a carcinogenic risk to humans. EPA has classified fenitrothion as a Group E chemical, "evidence of noncarcinogenicity for humans" (U.S. EPA, 1995, 1999a). Evidence from animal studies suggests that fenitrothion is not carcinogenic in animals.

TOXICOKINETICS

Fenitrothion is readily absorbed from the intestinal tract of most mammalian species, with about 90 to 100 percent of the dose absorbed (IPCS, 2000; EXTOXNET, 1995). In rats, oral absorption is approximately 90 to 100 percent within 72 hours, while in humans, it is about 70 percent in 96 hours (IPCS, 2000). Within 24 hours of dermal application, about 45 percent of the applied dose is absorbed (WHO, 2004; IPCS, 2000). In rats, a dermal absorption rate of slightly over 1 percent is suggested as fenitrothion disappeared rapidly during the first hour (EXTOXNET, 1995). Fenitrothion is widely distributed in the body. In rats, the highest concentrations after 48 hours are found in the liver, kidneys, and fat. It is rapidly activated and deactivated (IPCS, 2000). In the liver, fenitrothion is activated by oxidative desulfuration to the activated metabolite fenitrooxon (WHO, 2004; IPCS, 2000). It is then rapidly degraded by demethylation and hydrolysis into the inactive metabolites 3-methyl-4-nitrophenol and dimethylphosphate. Further oxidation to 3-carboxyl-4-nitrophenol is involved in a minor metabolic pathway. In dermally exposed rats, the area of highest concentration (other than skin) of fenitrothion after 31 hours was the cartilaginous part of the bones (EXTOXNET, 1995). Within 24 hours of oral exposures, up to 93 percent of the dose is excreted via the urine, and 5 to 15 percent is excreted in the feces (WHO, 2004; IPCS, 2000; U.S. EPA, 1995). In rats, rabbits, and dogs, seventeen metabolites have been isolated in the urine, and the parent compound was not detected (U.S. EPA, 1995).

Toxicokinetic studies in humans have shown the time to maximal plasma concentration was 1 hour in volunteers who ingested two capsules 12 hours apart that contained 0.09 or 0.18 mg fenitrothion/kg body weight for 4 days. The elimination half-time ranged from 2 to 3 hours for both doses. The maximal plasma concentration following a single oral dose was 0.09 mg/kg body weight 1 day after exposure and 0.84 ng/mL 4 days after exposure. Higher doses resulted in higher maximal concentrations on days 1 and 4 after exposure (1.8 ng/mL and 7.7 ng/mL, respectively). In addition, the elimination half-time of fenitrothion was 2 to 4.5 hours (WHO, 2004; IPCS, 2000). Human studies also indicate that fenitrothion does not accumulate. In humans, doses of 2.5 and 5 mg/man/day administered for 5 days were all excreted within 12 hours without accumulation. Urinary excretion of the metabolite 3-methyl-4-nitrophenol was almost complete within 24 hours in subjects given single oral doses of approximately 0.042 to 0.33 mg/kg body weight fenitrothion. Peak excretion occurred after 12 hours and plasma cholinesterase inhibition was seen in only one subject at the highest dose (EXTOXNET, 1995).

ECOLOGICAL EFFECTS

ACUTE EXPOSURE

Fenitrothion has been shown to be moderately to highly toxic to birds (WHO, 2004; U.S. EPA, 1995) and highly toxic to honeybees (U.S. EPA, 1995). It is also toxic to spider mites and has a long residual action (EXTOXNET, 1995). The toxicity of fenitrothion in birds ranges from highly toxic in game birds to slightly toxic in waterfowl. The oral LC_{50} in pheasants was reported as 450–500 ppm for 2-week-old pheasants fed fenitrothion in the diet for 5 days (EXTOXNET, 1995). In bobwhite quail, an LC_{50} of 157 ppm and an LD_{50} of 23.6 mg/kg have been reported (U.S. EPA, 1995; EXTOXNET, 1995). An LD_{50} of 1,190 mg/kg is reported in mallard ducks (EXTOXNET, 1995). The oral LD_{50} for chickens is reported as 28 mg/kg and fenitrothion was negative for delayed neurotoxicity in hens (EXTOXNET, 1995). In honeybees, the oral LD_{50} is reported between 0.02 and 0.38 µg/bee. In mammals, the acute oral toxicity data indicate that fenitrothion is moderately toxic to small mammals. Fenitrothion was acutely toxic to rats at 330 to 355 mg/kg (U.S. EPA, 1995). Additionally, fenitrothion was acutely toxic to mule deer at 727 mg/kg (EXTOXNET, 1995).

Fenitrothion has been shown to be moderately toxic to both warm and coldwater fish (WHO, 2004; U.S. EPA, 1995). Acute 96-hour LC_{50} values range from 1.7 ppm for brook trout to 3.8 ppm for bluegill sunfish, while the 48-hour LC_{50} ranges from 2.0 to 4.1 mg/L in carp. In various North American freshwater fish, the 96-hour LC_{50} values range from 2 to12 µg/L (EXTOXNET, 1995). Studies have shown that the toxicity of fenitrothion in rainbow trout was dependent on the developmental stage of the fish during exposure and the water temperature. Fingerlings and adult fish were the most sensitive, the sacfry stage was intermediate, and embryos were least sensitive to the toxic effects of fenitrothion. Additionally, the toxicity increased as water temperatures increased. In fish, sublethal effects of fenitrothion exposure include morphological and anatomical changes, behavioral changes, biochemical changes, respiratory effects, and effects on growth (EXTOXNET, 1995). Because fenitrothion breaks down rapidly, it does not accumulate in fish (WHO, 2004).

Fenitrothion is highly toxic in freshwater invertebrates. Acute exposure to 95 percent fenitrothion resulted in EC_{50}/ LC_{50} values ranging from 4.3 ppb in *Gammarus* to 11 ppb in *Daphnia magna* (U.S. EPA, 1995). It is also moderately to very highly toxic to estuarine organisms. Acute exposure to 75 percent fenitrothion resulted in EC_{50}/ LC_{50} values ranging from 1.5 ppb in pink shrimp to > 1,000 ppb in Sheepshead minnow (U.S. EPA, 1995).

CHRONIC EXPOSURE

Chronic toxicity data for non-target terrestrial organisms are limited. Fenitrothion has been shown to cause reproductive impairment in birds. Chronic exposure to 17 ppm fenitrothion reduced egg production in bobwhite quail, with a NOEL of 13 ppm (U.S. EPA, 1995).

Limited data for chronic duration exposures of aquatic organisms were located. In fish, the chronic toxicity of fenitrothion is generally considered to be low (EXTOXNET, 1995). In freshwater fish, studies have reported effects in rainbow trout chronically exposed to 94.5 percent fenitrothion. A LOEL of 88 ppb was determined for weight and length effects, with a NOEL of 46 ppm. In freshwater aquatic invertebrates, chronic exposure to 94.5 percent fenitrothion resulted in a 21 day LOEL of 0.23 ppb for adult daphnid survival in *Daphnia magna* with a NOEL of 0.087 ppb (U.S. EPA, 1995).

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PROFILE FOR FENTHION

CAS REGISTRY NUMBER 55-38-9

CHEMICAL SUMMARY

Fenthion (O,O-dimethyl O-[4-(methylthio)-m-tolyl] phosphorothiotate) is an organophosphate insecticide/acaricide/miticide. It is used as a contact and systemic agent for mosquito and insect control; for lice control on cattle and hogs; for control of insects and mites in horticulture; and in the past for bird control. It was first registered in 1965. A Registration Standard was issued in June 1988. In the Registration Standard, EPA classified all fenthion end-use products as Restricted Use pesticides based on avian, fish and aquatic invertebrate toxicity. Currently in the US it is only used to control adult mosquitos in Florida, and dragonfly larvae in ornamental fish ponds in Arkansa, Florida, and Missouri. Use as a mosquito larvicide has been voluntarily cancelled in the US (EPA 2001).

Fenthion toxicity in animals is based upon binding to and inhibition of the enzyme acetylcholinesterase (AChE). Inhibition of AChE leads to accumulation of acetylcholine, and interferes with proper neurotransmission in cholinergic synapses and neuromuscular junctions, which in turn can lead to sublethal effects and mortality. The effects of fenthion have been studied extensively in human, mammalian (e.g., rats, pigs, cattle, goats, monkeys) (EPA 2001, WHO 1995), and nonmammalian species (e.g., birds, fish and aquatic/terrestrial invertebrates) (EPA 1996). AChE inhibition is generally used as the most sensitive dose-response endpoint, and the potential for neurodevelopmental effects has been assessed in humans. Larger doses can result in death, respiratory distress, cardiovascular effects, and musculosketal effects; all largely related to AChE inhibition. There is no evidence of fenthion carcinogenicity.

HUMAN HEALTH EFFECTS

DATA QUALITY AND QUANTITY

Fenthion has been studied and reviewed in terms of human toxicity. Due to its limited current use in the US, it does not appear to have been recently reviewed by EPA. Key recent regulatory reports include the following:

- EPA 2001. Interim Reregistration Eligibility Decision for Fenthion.
- EPA 2016. Human Health Benchmarks for Pesticides. Fenthion.
- WHO 1995. Fenthion. Pesticide Residues in Food.
- WHO 1997. WHO 1995. Fenthion. Pesticide Residues in Food.
- WHO 2006. WHO Specifications and Evaluations for Public Health Pesticides: Fenthion

Fenthion is also listed in EPA's Human Health Benchmarks for Pesticides database (https://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home).

A 2005 US Agency for Toxic Substances Disease Registry (ATSDR) report on fenthion is cited in many other reports, but this report was not located on the ATSDR website or elsewhere.

TOXICITY

The World Health Organization (WHO) has established Acceptable Daily Intakes (ADIs) for fenthion. The toxicology of fenthion was first evaluated in 1971. In 1980, an ADI of 0 to 0.001 mg/kg was established on the basis of a no observed adverse effect level (NOAEL) of 0.009 mg/kg/d in a 2-year feeding study in dogs. The latest (WHO 1995) chronic ADI is 0 to 0.007 mg/kg/d, based upon a NOAEL from a 4-week study in humans, and including a 10-fold safety factor. An acute reference dose was established in 1997 (WHO 1997) as 0.01 mg/kg/d (based upon a NOAEL of 1 mg/kg/d in rats), which includes a 100-fold safety factor.

EPA's latest evaluation (EPA 2001) of human health risks notes that a 28-d human study was available, but that this was not employed (as "it is current Agency policy to make no final regulatory decision based on a human study until a new policy has been developed to ensure that such studies meet the highest scientific and ethical standards. This new policy is not yet in place, so the Agency has selected doses and endpoints to calculate dietary and non-dietary risk based solely on animal studies"). Instead, EPA used a 2-year monkey feeding study. EPA derived an acute dietary Population Adjusted Dose (PAD; equivalent in this case to a reference dose or RfD), based upon a NOAEL of 0.07 mg/kg/d and an endpoint of AChE inhibition at 1 week. A 100 fold uncertainty factor (UF) was applied (10 for interspecies, and 10 for intraspecies) to result in a PAD/RfD of 0.0007 mg/kg/d. EPA derived a chronic dietary PAD/RfD based upon a NOAEL/LOAEL of 0.02 mg/kg/d and the same endpoint. A 300 fold UF was applied (10 for interspecies, 10 for intraspecies, and 3 for lack of a true NOAEL) to result in a PAD/RfD of 0.00007 mg/kg/d. EPA also determined NOAELs/LOAELs for dermal and inhalation pathways (see Table 3a in EPA 2001) from this monkey feeding study, but did not estimate PADs/RfDs for these pathways. Given that the UFs described above are "generic", these were applied to the toxicity values in the table below to estimate benchmarks for dermal and inhalation exposures.

Differences between the WHO ADIs and the EPA RfDs are likely due to differences in data employed, as well as differences in UFs.

HUMAN TOXICITY BENCHMARK SUMMARY

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute	Oral	0.0007	mg/kg/d	RfD, unknown study and endpoint[1]	EPA 2016
Chronic	Oral	0.00007	mg/kg/d	RfD, unknown study and endpoint[1]	EPA 2016
Acute	Oral	7	ppb	HHBP, unknown study and endpoint[1]	EPA 2016
Chronic	Oral	0.5	ppb	HHBP, unknown study and endpoint[1]	EPA 2016
Acute	Oral	0.0007	mg/kg/d	NOAEL of 0.07 mg/kg/d based upon lack of plasma AChE inhibition at week 1 of a 2-year oral monkey study. A UF of 100 was applied to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations).	EPA 2001
Chronic	Oral	0.00007	mg/kg/d	LOAEL of 0.02 mg/kg/d based upon plasma AChE inhibition in 2-year oral monkey study. A UF of 300 was applied to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations, 3x lack of true NOAEL).	EPA 2001

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute	Oral	0.01	mg/kg/d	NOAEL of 1.0 mg/kg in rats, with a safety factor of 100.	WHO 1997
Chronic	Oral	0.007	mg/kg/d	NOAEL of 0.07 mg/kg/d in a four-week study of male volunteers, no inhibition of AChE. ADI of 0-0.007 mg/kg was established on the basis of the NOAEL, using a safety factor of 10. The ADI provides a margin of safety of > 100-fold for chronic ocular toxicity and for reproductive toxicity observed in rodents.	WHO 1995

1: The website https://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home:229002600293031 4 is intended to have a link to documentation for the fenthion RfDs, but this was not active; i.e., "page not found"). Presumably the studies and endpoints are the same as EPA 2001.

Abbreviations: AChE= acetylcholinesterase, ADI= acceptable daily intake, FQPA= Food Quality Protection Act, HHBP= human health benchmark for pesticides (in water), NOAEL= no observed adverse effect level, RfD= reference dose, UF=uncertainty factor

ECOLOGICAL EFFECTS

DATA QUALITY AND QUANTITY

EPA is currently conducting Biological Evaluations (BEs) for assessing risks to threatened and endangered species from selected pesticides. These BEs include many types of terrestrial, aquatic (both freshwater and marine), and avian animal species; as well as plants. At this time, a BE for fenthion does not appear to be available. There do not appear to be comprehensive regulatory reviews of fenthion ecological effects, likely because of its limited use compared to other similar pesticides.

The majority of studies and information are available for aquatic toxicity, as described below.

ENVIRONMENTAL BEHAVIOR

Fenthion's use as an insecticide (typically sprays or dusts) will result in its direct release to the environment. If released to the atmosphere, fenthion will degrade rapidly by reaction with photochemically produced hydroxyl radicals (half-life approximately 5 hr). When released to soil or water, fenthion will degrade through photodegradation and biodegradation. The persistence half life of fenthion in water under field conditions has been reported to range from 2.9 to 21.1 d for ocean, river, swamp, lake and canal waters. However, it may be more persistent in some environments where light and oxygen are limited. The soil half-life is 34 d. Fenthion is expected to have very low soil mobility, based upon a K_{oc} of 1500 (NLM 2016).

The primary degradation products are organochlorine compounds and carbon dioxide. If released into water, fenthion is expected to adsorb to suspended solids and sediment.

Bioconcentration information is limited. Using a flow-through system and up to 11 d of exposure, a mean bioconcentration factor (BCF) of 16,600 was measured in guppies (Poecilia reticulata). Based upon a measured Log K_{ow} of 4.09 and a water solubility of 7.5 mg/l at 20 deg C, the BCF of fenthion can be estimated to be 760 and 200, respectively, from regression derived equations. A fenthion BCF of 62 was measured in tadpoles after a 96 hr exposure period in a flow-through system (NLM 2016).

TOXICITY

Fenthion has been studied and reviewed in terms of aquatic toxicity under the Clean Water Act. The following values are from the EPA Office of Pesticide Programs database (at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/aquatic-life-benchmarks-pesticide-registration).

ECOLOGICAL TOXICITY BENCHMARK SUMMARY

Duration	Species	Value	Units	Endpoint
Acute	Fish	415	ug/L	Toxicity value x LOC. For acute fish, toxicity value is generally the lowest 96-hour LC50 in a standardized test (usually with rainbow trout, fathead minnow, or bluegill), and the LOC is 0.5.
Chronic	Fish	7.5	ug/L	Toxicity value x LOC. For chronic fish, toxicity value is usually the lowest NOEAC from a life-cycle or early life stage test (usually with rainbow trout or fathead minnow), and the LOC is 1.
Acute	Invertebrates	2.6	ug/L	Toxicity value x LOC. For acute invertebrate, toxicity value is usually the lowest 48- or 96-hour EC50 or LC50 in a standardized test (usually with midge, scud, or daphnids), and the LOC is 0.5.
Chronic	Invertebrate	0.013	ug/L	Toxicity value x LOC. For chronic invertebrates, toxicity value is usually the lowest NOAEC from a life-cycle test with invertebrates (usually with midge, scud, or daphnids), and the LOC is 1.
Acute	Nonvascular Plants	400	ug/L	Toxicity value x LOC. For acute nonvascular plants, toxicity value is usually a short-term (less than 10 d) EC50 (usually with green algae or diatoms), and the LOC is 1.
Acute	Vascular Plants	2800	ug/L	Toxicity value x LOC. For acute vascular plants, toxicity value is usually a short-term (less than 10 d) EC50 (usually with duckweed) and the LOC is 1.

Notes:

Values from https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/aquatic-life-benchmarks-pesticide-registration

Abbreviations: EC_{50}= 50% effect concentration, LC_{50}= 50% lethal concentration, LOC=level of concern, n/a= not available, NOAEC=no observed adverse effect concentration

The ecological data annex (D-4) contains further information on ecological toxicity values.

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PROFILE FOR LAMBDA-CYHALOTHRIN:

CAS REGISTRY NUMBER 91465-08-6

SUMMARY

CHEMICAL HISTORY

The synthetic pyrethroid lambda-cyhalothrin is a relatively new addition to this insecticide group. It was developed in 1977 and consists of one enantiomeric (i.e., nonsuperimposable, mirror image) pair of isomers and is a more biologically active form than cyhalothrin (IPCS, 1990a). It is used in the control of pests, including mosquitoes, in agricultural and public and animal health settings (EXTOXNET, 1996). The risks of occupational exposures and exposures to the general public are expected to be very low if proper precautions are followed. At the recommended application rates, lambda-cyhalothrin is not expected to cause adverse environmental effects. As is typical of synthetic pyrethroids, the typical symptoms for acute exposure are neurological and include tingling, burning, or numbness sensations (particularly at the point of skin contact), tremors, incoordination of movements, paralysis or other disrupted motor functions. These effects are generally reversible because lambda-cyhalothrin beaks down rapidly in the body (IPCS, 1990a; EXTOXNET, 1996).

DESCRIPTION OF DATA QUALITY AND QUANTITY

Lambda-cyhalothrin and cyhalothrin are basically the same chemical and differ only in their stereo chemistry and the number of isomers in each mixture (U.S. EPA, 2002a). Cyhalothrin consists of four stereo isomers while lambda-cyhalothrin is a mixture of only two isomers. The two lambda-cyhalothrin isomers are contained in cyhalothrin and they represent 40 percent of the cyhalothrin mixture. The majority of toxicity studies available were conducted using cyhalothrin as the test chemical. Evidence based on subchronic studies in rats suggests that the two mixtures are not biologically different with respect to their mammalian toxicity (U.S. EPA, 2002a).

EPA and ATSDR have developed quantitative human health benchmarks for cyhalothrin (EPA's acute and chronic oral RfDs and short-, intermediate-, and long-term dermal and inhalation benchmarks, and ATSDR's acute and intermediate oral MRLs).

Recommended resources include:

- Environmental Health Criteria 99: Cyhalothrin (IPCS, 1990a)
- Toxicological Profile for Pyrethrin and Pyrethroids (ATSDR, 2003a)
- Pesticide Information Profiles (PIP) for Lambda-cyhalothrin (EXTOXNET, 1996)
- Specifications and Evaluations for Public Health Pesticides for Lambda-cyhalothrin (WHO, 2003)
- Integrated Risk Information System (IRIS) summary review for cyhalothrin (U.S. EPA, 2005b).

SUMMARY TABLE

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute, Intermediate, Chronic	Inhalation	0.0008	mg/kg/day	Inhalation NOAEL for neurotoxicity in rats at 0.08 mg/kg/day (0.3 µg/L) with uncertainty factor (UF) of 100 applied	U.S. EPA (2002b)
Acute	Oral	0.005	mg/kg/day	Acute RfD based on neurotoxicity in dogs	U.S. EPA (2002b)
Intermediate	Oral	0.001	mg/kg/day	Adopt chronic RfD for intermediate duration	
Chronic	Oral	0.001	mg/kg/day	Chronic RfD based on neurological effects in dogs	U.S. EPA (2002b)
Acute, Intermediate, Chronic	Dermal	0.1	mg/kg/day	Dermal NOAEL in rats with UF of 100 applied	U.S. EPA (2002b)

For inhalation exposure, a NOAEL of 0.3 µg/L (0.08 mg/kg/day) was identified for neurotoxicity, decreased body weight, and slight changes in urinalysis parameters in rats exposed to lambda-cyhalothrin via inhalation for 21 days. An uncertainty factor of 100 was applied, for an inhalation benchmark value of 0.0008 mg/kg/day. This value is appropriate for all exposure durations (U.S. EPA, 2002a).

For oral exposure, an acute RfD of 0.005 mg/kg/day was derived based on a NOAEL of 0.5 mg/kg/day for neurotoxicity (ataxia) observed in dogs exposed to lambda-cyhalothrin, with an uncertainty factor of 100 applied (U.S. EPA, 2002a). A chronic oral RfD of 0.001 mg/kg/day was derived based on a NOAEL of 0.1 mg/kg/day for gait abnormalities in dogs exposed to lambda-cyhalothrin, with an uncertainty factor of 100 applied (U.S. EPA, 2002a). The chronic RfD was adopted to represent intermediate exposures.

For dermal exposure, a NOAEL of 10 mg/kg/day was identified in rats dermally exposed to lambda-cyhalothrin for 21 days. An uncertainty factor of 100 was applied, for a dermal benchmark value of 0.1 mg/kg/day. This value is appropriate for all exposure durations (U.S. EPA, 2002a).

BACKGROUND

CAS #:	91465-08-6
Synonyms:	none (WHO, 2003)
Chemical Group:	synthetic pyrethroid
Registered Trade Names:	Charge, Excaliber, Grenade, Karate, Hallmark, Icon, OMS 0321, PP321, Saber, Samurai, Sentinel, and Matador (EXTOXNET, 1996)

USAGE

Lambda-cyhalothrin is a synthetic pyrethroid (IPCS, 1990a) most commonly used for pest control, especially mosquitoes; the insecticide is usually sprayed on interior walls or used to impregnate bed nets (EXTOXNET, 1996). This insecticide is a restricted use pesticide, so it can be purchased and used only by certified

applicators (EXTOXNET, 1996). Lambda-cyhalothrin has adulticidal, ovicidal, and larvicidal activity (IPCS, 1990a). In addition to mosquitoes, it is effectively used to control: cockroaches, ticks, fleas, aphids, Colorado beetles, cutworms and butterfly larvae (EXTOXNET, 1996; IPCS, 1990a).

FORMULATIONS AND CONCENTRATIONS

There are several formulations for lambda-cyhalothrin, each containing varying amounts of the active ingredient. The typical formulations for lambda-cyhalothrin are

- Technical grade (not less than 810 g/kg lambda-cyhalothrin)
- Emulsifiable concentrate (at 20 +/- 2°C: up to 25 g/l +/- 15% declared content; > 25 g/l to 100 g/l +/- 10% of declared content)
- Wettable powder (up to 25 +/- 15% of declared content: > 25-100 +/- 10 % of declared content)
- Slow release capsule suspension (at 20 +/- 2°C: up to 25 g/l +/- 15% declared content).

The main formulation used for agricultural purposes is the emulsifiable concentrate. The wettable powder formulation is mainly used for public health reasons (WHO, 2003). Lambda-cyhalothrin is commonly mixed with buprofezin, pirimicarb, dimethoate, or tetramethrin, resulting in the usual product (WHO, 2003; EXTOXNET, 1996).

SHELF-LIFE

This insecticide, like many others, needs to be stored in a cool, dry, and well-ventilated facility (IPCS, 1990a). Lambda-cyhalothrin should not be stored or transported with foodstuffs and household supplies to the limit the potential for cross contamination and human exposure (IPCS, 1990a).

DEGRADATION PRODUCTS

In the environment, lambda-cyhalothrin degrades through biological and photochemical reactions (IPCS, 1990a). Biological reactions are thought to be more important. Lambda-cyhalothrin will degrade rapidly in soils, remain relatively stable in water, and is usually not found in air due to its low vapor pressure. The main degradation products are 3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2, 2-dimenthyl-cyclopropanecorboxylic acid, the amide derivative of cyhalothrin, and 3-phenoxybenzoic acid. The degradation is a result of the cleavage of the ester linkage to give two main degradation products, which are further degraded to carbon dioxide. Lambda-cyhalothrin degrades fairly quickly in alkaline conditions, in comparison to neutral or acidic media. It is strongly absorbed in soils and sediments with little tendency for bioaccumulation (IPCS, 1990a).

In water, lambda-cyhalothrin is stable at pH 5. Racemization at the alpha-cyano carbon occurs at pH 7 to pH 9, creating a one to one mixture of enantiomer pairs A and B. The ester bond is hydrolysed at pH 9. Additionally, a moderately high rate of photolysis is seen in dilute aqueous solutions (IPCS, 1990a).

ENVIRONMENTAL BEHAVIOR

FATE AND TRANSPORT IN TERRESTRIAL SYSTEMS

In most soil types, lambda-cyhalothrin is not very mobile. Its high reported organic carbon partitioning coefficient (Koc) value reflects its strong affinity for soil. It is retained more in soil with low sand content or high organic matter content (EXTOXNET, 1996). Studies have shown that lambda-cyhalothrin and its degradation products do not leach through soils into groundwater nor are they transported to other compartments of the environment following agricultural uses (IPCS, 1990a).

Lambda-cyhalothrin is moderately persistent in soil with a soil half-life ranging from 4 to 12 weeks. A longer in-field half-life of approximately 30 days is reported for most soils (EXTOXNET, 1996). The half-life is variable because it is dependent on the availability of sunlight, which speeds degradation (IPCS, 1990a).

FATE AND TRANSPORT IN AQUATIC SYSTEMS

Lambda-cyhalothrin is not expected to be prevalent in surface or groundwater because it has extremely low water solubility and binds tightly to soil. Lambda-cyhalothrin enters surface water largely through surface runoff. Even so, lambda-cyhalothrin is most likely to stay bound to sediment and settle to the bottom. Studies have shown that hydrolysis of lambda-cyhalothrin occurs rapidly at a pH of 9 but not at a pH of 7, though isomerization was observed at a pH of 7. No hydrolysis or isomerization was seen at a pH of 5.

HUMAN HEALTH EFFECTS

ACUTE EXPOSURE

Effects/Symptoms

No data on accidental human poisonings have been reported. Additionally, no quantitative epidemiological studies are available (IPCS, 1990a). However, under normal use conditions, acute exposure to lambda-cyhalothrin is not expected to represent a hazard in humans. Transient skin sensations such as periorbital facial tingling and burning have been reported following direct skin exposure in laboratory workers and manufacturing workers handling synthetic pyrethroids. This sensation is possibly due to repetitive firing of sensory nerve terminals and usually lasts for a few hours up to 72 hours post-exposure. No neurological abnormalities have been observed upon medical examination (IPCS, 1990a). Lambda-cyhalothrin can irritate the eyes, skin, and upper respiratory tract. Additionally, oral exposure can cause neurological effects, including tremors and convulsions. Ingestion of liquid formulations may result in aspiration of the solvent into the lungs, resulting in chemical pneumonitis. Based on the acute oral toxicity data, lambda-cyhalothrin has been classified as "Moderately Hazardous" (Class II) (WHO, 2003).

In animals, the technical form of lambda-cyhalothrin is moderately toxic; however, toxicity depends on both the formulation (concentration of active ingredient and solvent vehicle) and the route of exposure (EXTOXNET, 1996). Laboratory data indicate that acute oral exposure to lambda-cyhalothrin is moderately to highly toxic in rats and mice and that mice are more susceptible to the toxic effects than rats (WHO, 2003). The oral LD_{50} for lambda-cyhalothrin in corn oil has been reported to range from 56 mg/kg in female rats up to 79 mg/kg in males. A similar LD_{50} is reported for technical grade lambda-cyhalothrin in rats at 64 mg/kg (EXTOXNET, 1996). The oral LD_{50} in mice is reported as 20 mg/kg (IPCS, 1990a). The effects of acute oral exposure are typical of pyrethroid toxicity, including abnormal motor function (WHO, 2003).

Acute inhalation exposures are also highly toxic to animals (WHO, 2003). In the formulated product Karate, the 4-hour LC_{50} in rats is reported as 0.175 mg/L in females and 0.315 mg/L in males (EXTOXNET, 1996).

Lambda-cyhalothrin is less toxic in animals via acute dermal exposure (WHO, 2003). In rats, dermal LD_{50}s of 632 mg/kg for males and 696 mg/kg for females have been reported for the technical product. Studies have also shown the technical product produced no skin irritation to rabbits and is nonsensitizing in guinea pigs. Mild eye irritation was observed in rabbits. However, dermal exposure to the formulated product Karate causes severe primary skin irritation in rabbits and mild skin sensitization in guinea pigs. Other acute dermal effects are related to the nervous system and include tingling, burning sensations, or numbness (EXTOXNET, 1996).

Treatment

Lambda-cyhalothrin and its breakdown products can be detected in blood and urine, but only within a few days of the last exposure (ATSDR, 2003a). Dermal exposure to lambda-cyhalothrin exposure should be treated by removing contaminated clothing and washing the exposed areas with soap and water. If lambda-cyhalothrin gets into the eyes, they should be rinsed with water for several minutes. Contact lenses should be removed if possible and medical attention should be sought. Vomiting should not be induced following ingestion of lambda-cyhalothrin, and medical attention sought. Inhalation exposures require removal to fresh air and rest (IPCS, 1990b)

CHRONIC EXPOSURE

NONCANCER ENDPOINTS

Based on the available data, it is unlikely that lambda-cyhalothrin would cause chronic effects in humans under normal conditions. No specific target organs have been identified in the available chronic studies (EXTOXNET, 1996). Decreased body weight gain and mild neurological effects have been observed in some animal studies (EXTOXNET, 1996; IPCS, 1990a).

Lambda-cyhalothrin is not expected to be teratogenic, mutagenic, or genotoxic in humans. Studies in animals have found no teratogenic or fetotoxic effects in rats or rabbits. Additionally, it was negative in five test strains in the Ames mutagenicity assay (IPCS, 1990a). No mutagenic or genotoxic effects were seen in other in vitro cytogenic assays or chromosomal aberration tests (EXTOXNET, 1996).

CANCER ENDPOINTS

Data on the carcinogenic potential suggest that lambda-cyhalothrin is not carcinogenic in humans. In rats and mice exposed to cyhalothrin, no carcinogenic effects were observed. EPA has classified lambda-cyhalothrin as a Group D chemical, "not classifiable as to human carcinogenicity" (U.S. EPA, 2002a).

TOXICOKINETICS

Animal studies have been have been conducted in various species to investigate the toxicokinetics of cyhalothrin and lambda-cyhalothrin. Oral cyhalothrin is readily absorbed, metabolized thoroughly, and eliminated as polar conjugates in the urine (IPCS, 1990a). Studies with lambda-cyhalothrin have shown that it also is rapidly metabolized into less toxic water-soluble compounds and excreted in the urine and feces (EXTOXNET, 1996). In mammals, cyhalothrin is metabolized as a result of ester cleavage to cyclopropanecarboxylic acid and 3-phenoxybenzoic acid, and eliminated as conjugates. Tissue levels decline after exposure stops and residues in the body are low (IPCS, 1990a).

ECOLOGICAL EFFECTS

ACUTE EXPOSURE

Toxicity to Non-Target Terrestrial Organisms

Like other synthetic pyrethroids, lambda-cyhalothrin has been shown to be toxic to honey bees but has little effect on birds and domestic animals (EXTOXNET, 1996). In birds, the toxicity of lambda-cyhalothrin ranges from nontoxic to slightly toxic. Oral LD_{50} values in mallard duck are reported as greater than 3,950 mg/kg. Dietary LC_{50} values of 5,300 ppm are reported in bobwhite quail. Additionally, there is no evidence of lambda-cyhalothrin accumulation in bird tissues or in eggs (EXTOXNET, 1996). Lambda-cyhalothrin has shown mixed toxicity to other non-target terrestrial organisms. It is extremely toxic to honey bees, with a

contact LD_{50} of 0.9 µg/bee and an oral LD_{50} of 38 ng/bee (EXTOXNET, 1996), but has no adverse effect on earthworms (IPCS, 1990a).

Toxicity to Aquatic Organisms

Like other synthetic pyrethroids, lambda-cyhalothrin has been shown to be quite toxic under laboratory conditions to both cold and warm water fish. Acute 96-hr LC_{50} values range from 0.2 to 1.3 µg/L. It is also highly toxic to aquatic arthropods with 48-hr LC_{50} ranging from 0.008 to 0.4 µg/L (IPCS, 1990a; WHO, 2003). In the field, however, these effects are not likely to occur under the recommended use scenarios (WHO, 2003). No serious adverse effects have been observed due to the low rates of application and the lack of persistence in the environments (IPCS, 1990a). Accumulation studies have shown that although bioaccumulation is possible in fish, it is unlikely due to the rapid metabolism of lambda-cyhalothrin (EXTOXNET, 1996).

CHRONIC EXPOSURE

Toxicity to Non-Target Terrestrial Organisms

No data were located on the chronic toxicity to non-target terrestrial organisms.

Toxicity to Aquatic Organisms

No data for chronic duration exposures of aquatic organisms were located; however, a subchronic study in Sheepshead minnow embryos and larvae showed no effect on hatchability or larval survival when exposed to up to 0.25 µg/L through 28 days post hatching. A significant effect on larval weight was observed at 0.38 µg/L. In an additional subchronic exposure study, survival, growth, and reproduction of *Daphnia magna* were seen at 40 ng/L but not at 2.5 ng/L (IPCS, 1990a).

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PROFILE FOR MALATHION:

CAS REGISTRY NUMBER 121-75-5

SUMMARY

CHEMICAL HISTORY

Malathion is an organophosphate pesticide used in a wide variety of applications, including agricultural, veterinary, and public health uses. In pest eradication programs, malathion is used to eradicate mosquitoes, Mediterranean fruit flies, and boll weevil (ATSDR, 2003b). The primary target of malathion is the nervous system; it causes neurological effects by inhibiting cholinesterase in the blood and brain. Exposure to high levels can result in difficulty breathing, vomiting, blurred vision, increased salivation and perspiration, headaches, and dizziness (U.S. EPA, 2005c). Loss of consciousness and death may follow very high exposures to malathion (ATSDR, 2003b).

DESCRIPTION OF DATA QUALITY AND QUANTITY

Several comprehensive reviews on the toxicity of malathion have been prepared or updated in recent years:

- EPA risk assessment for the Reregistration Eligibility Decision (RED) document (U.S. EPA, 2005c)
- IRIS summary review (U.S. EPA, 2005d)
- *Toxicological Profile for Malathion* (ATSDR, 2003b)
- *Specifications and Evaluations for Public Health Pesticides for Malathion* (WHO, 2003).

EPA and ATSDR have developed quantitative human health benchmarks (EPA's acute and chronic oral RfDs, short-, intermediate-, and long-term dermal and inhalation benchmarks and ATSDR's acute inhalation and intermediate oral and inhalation MRLs).

SUMMARY TABLE

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute, Intermediate, Chronic	Inhalation	0.026	mg/kg/day	Inhalation LOAEL for respiratory effects in rats of 25.8 mg/kg/day (0.1 mg/L) with UF of 100 and SF of 10 applied	U.S. EPA (2005c)
Acute	Oral	0.14	mg/kg/day	Acute RfD based on neurological effects in rats	U.S. EPA (2005c)
Intermediate	Oral	0.03	mg/kg/day	Adopt chronic oral RfD for intermediate duration	
Chronic	Oral	0.03	mg/kg/day	Oral RfD based on neurological effects in rats	U.S. EPA (2005c)
Acute, Intermediate, Chronic	Dermal	0.05 (child) 0.5 (adult)	mg/kg/day	Dermal NOAEL for neurological effects in rabbits with UF of 100 applied (for children, an additional SF of 10 was also applied)	U.S. EPA, 2005c

For inhalation exposure, a LOAEL of 0.1 mg/L (25.8 mg/kg/day, assuming absorption via inhalation route is equivalent to oral absorption) for histopathological lesions in the nasal cavity and larynx of rats was identified for malathion. Uncertainty factors of 10 each were applied to account for interspecies and intrahuman variability and a safety factor of 10 to account for the extrapolation from LOAEL to NOAEL and the severity of effect (U.S. EPA, 2005c). This value is appropriate for short- (1–30 days) and intermediate-term (1–6 months) inhalation exposures; this value was also adopted for chronic (long-term, >6 months) exposures.

For oral exposure, an acute oral RfD of 0.14 mg/kg/day was derived based on the inhibition of red blood cell (RBC) cholinesterase in rats and uncertainty factors of 10 each to account for interspecies and intrahuman variability (U.S. EPA, 2005d). A chronic oral RfD of 0.03 mg/kg/day was derived based on the RBC cholinesterase inhibition in rats and uncertainty factors of 10 each to account for interspecies and intrahuman variability (U.S. EPA, 2005c).

For dermal exposures, a NOAEL of 50 mg/kg/day for plasma, RBC, and brain cholinesterase inhibition in rabbits exposed dermally was identified for malathion. Uncertainty factors of 10 each to account for interspecies and intrahuman variability were applied; a safety factor of 10 to account for susceptibility of young was applied to be protective of children (U.S. EPA, 2005d). This value is appropriate for short- (1–30 days), intermediate- (1–6 months), and long-term (>6 months) dermal exposures.

BACKGROUND

CASRN:	121-75-7
Synonyms:	1, 2-Di (ethoxycarbonyl) ethyl, *O, O*-dimethyl, phosphorodithioate (ATSDR, 2003b), maldison, malathon, mercaptothion, mercaptotion, carbofos (WHO, 2003)
Chemical Group:	organophosphate
Registered Trade Names:	Cekumal, Fyfanon®, Malixol®, Maltox® (ATSDR, 2003b); Celthion, Cythion, Dielathion, El 4049, Emmaton, Exathios, Fyfanon and Hilthion, and Karbofos (EXTOXNET, 1996)

USAGE

Malathion is a nonsystemic, broad-spectrum organophosphate insecticide used to control sucking and chewing pests in agricultural and horticultural applications (WHO, 2003). It is also used to control household insects, fleas, ectoparasites in animals, and head and body lice in humans (EXTOXNET, 1996). A major public health use of malathion is to eradicate mosquitoes and Mediterranean fruit flies, with ground application and aerial spraying being the most common methods of application (ATSDR, 2003b).

FORMULATIONS AND CONCENTRATIONS

There are several typical formulations for malathion, each formulation varying in the amount of active ingredient (ai) it contains. The typical formulations for malathion are (U.S. EPA, 2005c; ATSDR, 2003b)

- Technical grade (91–95 percent ai)
- Dust (1–10 percent ai)
- Emulsifiable concentrate (3–82 percent ai)
- Ready-to-use liquid (1.5–95 percent ai)

- Pressurized liquid (0.5–3 percent ai)
- Wettable powder (6–50 percent ai).

Malathion may also be used to formulate other pesticides (ATSDR, 2003b).

DEGRADATION PRODUCTS

In the United States, technical grade malathion is >90 percent pure and contains less than 5 percent impurities (reaction byproducts and degradation products). As many as 14 different impurities have been identified in technical grade malathion (ATSDR, 2003b), some of which are toxic themselves and potentiate the toxicity of malathion. Because of their toxicological properties, relevant impurities include malaoxon (CASRN 1634-78-2), isomalathion (CASRN 3344-12-5), MeOOSPS-triester (CASRN 2953-29-9), MeOOOPS-triester (CASRN 152-18-1), MeOSSPO-triester (CASRN 22608-53-3), and MeOOSPO-triester (CASRN 152-20-5). Both isomalathion and malaoxon are more toxic than malathion, and isomalathion is a potentiator of malathion (WHO, 2003). Degradation products of malathion include dimethyl phosphate, dimethyldithiophosphate, dimethylthiophosphate, isomalathion (a metabolite of malathion), malaoxon, and malathion dicarboxylic acid and are generally the result of impurities or exposure to extreme storage conditions (PAN, 2005).

In dustable powder form, malathion levels decrease when it is stored and it is converted into the more toxic metabolite isomalathion (WHO/FAO, nd). In the environment, malathion is usually broken down into other chemical compounds within a few weeks by water, sunlight and bacteria found in the soil and water (ATSDR, 2003b). At pH 5.0, malathion is reasonably stable to hydrolysis. It hydrolyzes rapidly at pH 7.0 and above or below pH 5.0 (WHO, 2003; ATSDR, 2003b). It is stable in an aqueous solution that is buffered at a pH of 5.26 (WHO/FAO, nd). In air, malathion is broken down by reacting with sunlight as well as other chemicals found naturally in the air (ATSDR, 2003b). Malathion is generally stable to photolysis (WHO, 2003).

SHELF LIFE

Malathion levels decline over time during storage. The extent of the decline depends on the type of formulation, as does the increase in isomalathion levels. Technical grade malathion stored at 20°C for 25–30 months lost 3–8 g/kg, while isomalathion levels increased 2.2-2.4 mg/kg. Levels of other impurities did not increase significantly. Malathion stored for 14 days at 54°C declined 2.6 percent as an emulsifiable concentrate, 2.8 percent as a emulsion (oil in water), and 5 percent as a dustable powder, while isomalathion levels increased 0.11 percent, 0.095 percent, and 1.35 percent, respectively (WHO, 2003).

ENVIRONMENTAL BEHAVIOR

FATE AND TRANSPORT IN TERRESTRIAL SYSTEMS

Malathion is released directly into the air during aerial application to target areas such as crops or residential areas. It may also be released via volatilization from crop and ground surfaces. Aerial applications may also release malathion into the soil by way of spray droplets that reach the surface of the soil. This may include spraying and fogging applications. Malathion may also be released into the soil as a consequence of wet deposition applications or when improperly disposed of (ATSDR, 2003b).

In air, malathion may be transported from the site of application to other areas by wind and precipitation. In soils, malathion is moderately to highly mobile, indicating a potential to readily move from soil into groundwater. However, because malathion degrades rapidly in the environment, movement from soil to groundwater is not a significant concern (ATSDR, 2003b).

Malathion degrades through atmospheric photo-oxidation, hydrolysis, and biodegradation. (ATSDR, 2003b). In the atmosphere, malathion breaks down rapidly in sunlight, with a half-life of 1.5 days. In soil, malathion is of low persistence with an average half-life of 6 days. It degrades rapidly depending on the degree of soil binding, which is generally moderate (EXTOXNET, 1996). Malathion degrades more quickly in moist soil (ATSDR, 2003b). The persistence of malathion in vegetation depends largely on the lipid content of the plant. The degradation process is increased with moisture content (EXTOXNET, 1996).

FATE AND TRANSPORT IN AQUATIC SYSTEMS

Malathion may be released into surface waters through direct applications, spills, runoff from sprayed areas, wet deposition from rain, manufacturing or processing facilities, and wastewater releases (ATSDR, 2003b). The water solubility of malathion is 148 mg/l at 25°C. At pH 5, it is reasonably stable to hydrolysis; however, as pH increases, malathion hydrolyses more readily (WHO, 2003). Because it is highly soluble and binds moderately to soil, malathion may also pose a risk to groundwater or surface waters (EXTOXNET, 1996).

In water, malathion degrades relatively quickly due to the action of the water as well as bacteria in the water (ATSDR, 2003b). In water, malathion breaks down into mono- and dicarboxylic acids. However, degradation also depends on the temperature and pH of the water. In river water, malathion breaks down in 1 week, while it is stable in distilled water for 3 weeks. Degradation increases with water temperature, alkalinity, and salinity of the water. Because of its short half-life in water, malathion is not expected to bioaccumulate in aquatic organisms (EXTOXNET, 1996).

HUMAN HEALTH EFFECTS

ACUTE EXPOSURE

Effects/Symptoms

Similar to other organophosphates, malathion is a cholinesterase inhibitor and interferes with the normal functioning of the nervous system. Malathion exhibits low acute toxicity via ingestion, dermal, and inhalation exposures (ATSDR, 2003b). Human volunteers fed very low doses of malathion for 6 weeks showed no significant effects on blood cholinesterase activity (ATSDR, 2003b). However, acute exposure to high concentrations can cause numbness, headaches, sweating, abdominal cramps, blurred vision, difficulty breathing, respiratory distress, loss of consciousness, and occasionally death. Acute exposure data for humans are limited and come from case reports of accidental poisonings (ATSDR, 2003b).

Several factors affect the toxicity of malathion, including the product purity, route of exposure, gender, and the amount of protein in the diet. Animal studies have shown that malathion is only slightly toxic following acute oral and dermal exposures, with reported LD_{50} values in rats of 1,000–10,000 mg/kg and 400–4,000 mg/kg, respectively. Additionally, as protein levels in the diet decrease, malathion toxicity increases. Females have been shown to be more susceptible to malathion toxicity than males due to differences in metabolism, storage, and excretion (EXTOXNET, 1996). It is uncertain whether children are more susceptible to the toxic effects of malathion; however, animal studies have shown that very young animals are more susceptible to the effects of malathion than older ones when exposed to high levels (ATSDR, 2003b). Weanling male rats acutely exposed to malathion were twice as susceptible to malathion as adults (EXTOXNET, 1996).

Treatment

Exposure to malathion may be determined through laboratory tests of urine and blood that measure breakdown products of malathion in urine or cholinesterase levels in blood (ATSDR, 2003b).

Long-term deleterious effects may be avoided if people exposed to high amounts of malathion are given the appropriate treatment quickly after exposure (ATSDR, 2003b). Oral exposure to malathion should be treated

with rapid gastric lavage unless the patient is vomiting. Dermal exposures should be treated by washing the affected area with soap and water. If the eyes have been exposed to malathion, flush them with saline or water. People exposed to malathion who exhibit respiratory inefficiency with peripheral symptoms should be treated via slow intravenous injection with 2–4 mg atropine sulfate and 1,000–2,000 mg pralidoxime chloride or 250 mg toxogonin (adult dose). Exposure to high levels of malathion that result in respiratory distress, convulsions, and unconsciousness should be treated with atropine and a reactivator. Morphine, barbiturates, phenothiazine, tranquillizers, and central stimulants are all contraindicated (WHO/FAO, nd).

CHRONIC EXPOSURE

NONCANCER ENDPOINTS

Most chronic human data come from studies of workers who are exposed to malathion via inhalation or dermally. Chronic exposure data in both humans and animals indicate that the main target of malathion toxicity is the nervous system (ATSDR, 2003b). A two-year rat study showed no adverse effects other than cholinesterase enzyme depression (EXTOXNET, 1996). Chronic animal studies have shown no reproductive or developmental toxicity at doses of malathion that are not maternally toxic. Malathion has been shown to be a contact sensitizer. Recent animal studies indicate that malathion can affect immunological parameters at doses that are lower than those that cause neurotoxicity (ATSDR, 2003b).

CANCER ENDPOINTS

EPA has classified malathion as "suggestive evidence of carcinogenicity" (U.S. EPA, 2005c). While some studies indicate an increased incidence of some forms of cancer in people who are regularly exposed to malathion, such as those exposed occupationally, there is no conclusive evidence that malathion causes cancer in humans. In one study, rodents fed very high doses of malathion in their diet had increased incidences of liver tumors (ATSDR, 2003b; U.S. EPA, 2005c).

TOXICOKINETICS

Malathion is absorbed via inhalation, the gastrointestinal tract, and dermally (WHO/FAO, 1997). Dermal absorption is dependent on the site and dose applied (ATSDR, 2003b). Malathion is broken down in the liver into metabolites. One of its metabolites is malaoxon, from which malathion exhibits its toxic effects via cholinesterase inhibition (ATSDR, 2003b; U.S. EPA, 2005c; WHO/FAO, 1997). Neither malathion nor its metabolites tend to accumulate in the body and are mostly excreted within a few days (ATSDR, 2003b). Malathion is excreted mostly in the urine with a small amount being excreted in the feces. A very small amount may also be excreted in breastmilk. Metabolites excreted include the monoacid and diacid of malathion, demethyl malathion, dimethyl phosphate, and O,O-dimethylphosphorothioate. In feces, the majority of material excreted is malathion with a smaller amount being malaoxon (WHO/FAO, 1997)

ECOLOGICAL EFFECTS

ACUTE EXPOSURE

Malathion is not expected to pose a hazard to birds and mammals from acute dietary exposure. Malathion exhibits low to moderate toxicity to birds (U.S. EPA, 2005e). Acute oral LD_{50} values in various bird species include blackbirds and starlings (over 100 mg/kg), pheasants (167 mg/kg), chickens (525 mg/kg), and mallards (1,485 mg/kg). Malathion is rapidly metabolized by birds, with 90 percent being excreted in the urine within 24 hours. The toxicity of malathion to reptiles has not been evaluated, but the avian toxicity thresholds have been used to estimate the hazard. Acute effects were reported in one study of the Carolina anole and another on developing snapping turtle embryos (U.S. EPA, 2005e). Malathion is extremely toxic to beneficial insects, including honeybees (U.S. EPA, 2005e; EXTOXNET, 1996).

Malathion also has a wide range of toxicity to species in the aquatic environment, from being quite toxic to walleye with a 96 hr LC_{50} of 0.06 mg/L to being slightly toxic in goldfish with a 96 hr LC_{50} of 10.7 mg/L (EXTOXNET, 1996). In invertebrates and amphibians in their aquatic stages, malathion is also found to be highly toxic. In aquatic invertebrates, EC_{50} values range from 1 µg/L to 1 mg/L. However, since malathion has a very short half-life, there is little potential for bioconcentration in aquatic organisms (EXTOXNET, 1996). Malathion is also highly toxic to the larvae of terrestrial, non-target insects that have aquatic early life stages (U.S. EPA, 2005e).

CHRONIC EXPOSURE

Although not persistent in the environment, birds may be chronically exposed because current labels do not restrict consecutive applications, intervals, or avoidance of nesting birds. Sublethal effects to birds may include reduced nesting behavior, disorientation, and loss of motor coordination. Studies have shown that chronic malathion exposure in the diet of terrestrial avian species causes moderate toxicity. Bobwhite quail exposed to 350 ppm for 10 weeks exhibited regressed ovaries, enlarged or flaccid gizzards, and a reduction in number of eggs that hatched. At higher exposures, a reduction in the number of eggs produced, viability of embryo, and an increase in cracked eggs was observed, while studies in waterfowl showed low toxicity (U.S. EPA, 2005e).

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PROFILE FOR METHOPRENE:

CAS REGISTRY NUMBER 40596-69-9

SUMMARY

CHEMICAL HISTORY

Methoprene is a larvicide and growth regulator that is used in agricultural, horticultural, and public health applications (HSDB, 2005; EXTOXNET, 1996). It is considered a biochemical pesticide because it acts by interfering with the life cycle of the insect instead through direct toxicity. It regulates growth by preventing insects from reaching maturity or reproducing (U.S. EPA, 2005, 2002, 2001, 1991a, 1991b; ATSDR, 2005; EXTOXNET, 1996; HSDB, 2005). Methoprene was first registered for use in the United States in 1975; there are currently 13 registered products. EPA has classified methoprene as toxicity class IV or slightly to almost nontoxic (EXTOXNET, 1996). In food production, methoprene is used on meat, milk, eggs, mushrooms, peanuts, rice, and cereals. As food additive, it prevents the breeding of hornflies in manure. In water, methoprene is used to control mosquito larvae as well as various flies, moths, beetles, and fleas (ATSDR, 2005; EXTOXNET, 1996; U.S. EPA, 2002, 2001, 1991a, 1991b). Methoprene is also used to on mammalian pets to control ectoparasites (U.S. EPA, 2005). It is available as a suspension, emulsifiable and soluble concentrate formulations, briquettes, pellets, sand granules, liquids aerosols, and bait (U.S. EPA, 2002; EXTOXNET, 1996).

Methoprene is selective, stable, and potent but not persistent in the environment or toxic to mammals. It presents no long-term hazard other than to the target species (U.S. EPA, 1991a, 1991b; WHO/FAO, n.d.). It has low potential for acute oral or inhalation toxicity. It is not a skin or eye irritant or skin sensitizer and is of low acute dermal toxicity. No adverse effects have been seen in humans or other non-target species (U.S. EPA, 2005, 2001, 1991a, 1991b). No chronic, oncogenetic, reproductive, developmental, or mutagenic effects have been seen in animals. In mammals it is rapidly and completely metabolized (U.S. EPA, 1991a). In mosquito control uses, there is little chance for human exposure because methoprene is applied directly to ditches, ponds, marshes, or flood areas that are not used for drinking water (U.S. EPA, 2002). Humans can be exposed to methoprene in small amounts through the food supply; through mixing, loading, or application of the pesticide; or while working with treated crops. Methoprene used in mosquito control does not pose a high risk of toxicity to wildlife or the environment. It is of low toxicity to birds and fish and nontoxic to bees; however, it is highly acutely toxic to aquatic invertebrates under laboratory conditions (U.S. EPA, 2005, 2002, 1991a, 1991b).

DESCRIPTION OF DATA QUALITY AND QUANTITY

An extensive toxicity database has been compiled for methoprene, which includes acute toxicity batteries, irritation/sensitization studies, subchronic feeding studies, developmental and reproductive toxicity studies, mutagenicity studies, chronic feeding studies, lifetime carcinogenicity studies, and special studies on metabolism and fate and potential for endocrine disruption (U.S. EPA, 2001). Reviews on the toxicity of methoprene have been prepared:

- Registration Eligibility Document Isopropyl (2E, 4E)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate (Referred to as Methoprene) (U.S. EPA, 1991a)
- Toxicologic Information About Insecticides Used for Eradicating Mosquitoes (West Nile Virus Control): Methoprene (ATSDR, 2005)
- Residues in Food – 1984. Toxicological Evaluations – Methoprene (WHO/FAO, 1984)

- Data Sheet on Pesticides No. 47. Methoprene (WHO/FAO, n.d.)
- Pesticide Information Profiles: Methoprene (EXTOXNET, 1996)
- The Pesticide Action Network (PAN) Pesticide Database (PAN, 2005).

SUMMARY TABLE

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute, Intermediate, Chronic	Inhalation	25	mg/kg/day	Inhalation NOAEL in rats with a UF of 100 applied	
Acute, Intermediate, Chronic	Oral	0.4	mg/kg/day	Chronic oral RfD based on liver effects in mice	U.S. EPA (1991a)
Acute, Intermediate, Chronic	Dermal	1	mg/kg/day	Dermal NOAEL of 100 mg/kg in rabbits with a UF of 100 applied	

For inhalation exposure, a NOAEL of 20 mg/L (21,000 mg/kg/day)[5] was identified in rats exposed to methoprene via inhalation for 4 hours per day, 5 days per week for 3 weeks (Olson and Willigan, 1972; ATSDR, 2005). The concentration was adjusted for intermittent exposure[6] (2,500 mg/kg/day) and an uncertainty factor of 100 was applied to account for interspecies and intrahuman variation, for an inhalation benchmark of 25 mg/kg/day. This value is appropriate for all exposure durations.

For oral exposure, a chronic oral RfD of 0.4 mg/kg/day was derived based on a NOAEL of 37.5 mg/kg/day for liver effects (pigmentation) in mice exposed to methoprene for 18 months (Wazeter and Goldenthal, 1975), with an uncertainty factor of 100 applied to account for interspecies and intrahuman variability (U.S. EPA, 1991a). The RfD was adopted to also represent acute and intermediate exposures.

For dermal expousre, a NOAEL of 100 mg/kg was identified in a 30-day rabbit study (Nakasawa et al., 1975). The LOAEL for the study was 300 mg/kg for erythema at the application site (ATSDR, 2005). An uncertainty factor of 100 was applied to account for interspecies and intrahuman variability. This value is appropriate for acute, intermediate, and chronic dermal exposures.

INSECTICIDE BACKGROUND

CASRN: 40596-69-9

Synonyms: isopropyl (E,E)-(RS)-11-methoxy-3,7,11-trimethyldodeca-2,4-dienoate, ZR-515; ENT-70460, 1-Methylethyl (E,E)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate, 2,4-Dodecadienoic acid, 11-methoxy-3,7,11-trimethyl-, 1-methylethyl ester, (E,E)- , 2,4-Dodecadienoic acid, 11-methoxy-3,7,11-trimethyl-, ispropyl ester, (E,E)-, Isopropyl (2E,4E)-11-methoxy-3,7,11-trimethyl-2,4-

[5] Conversion between mg/m^3 and mg/kg/day assumes, for Wistar rats (species not specified, but Wistars represent the median body weight for laboratory rats), an average body weight of 0.187 kg and inhalation rate of 0.2 m^3/day (U.S. EPA, 1988).

[6] Adjustment for intermittent exposure is the product of air concentration and exposure of 4/24 hours/day and 5/7 days/week.

	dodecadienoate, Isopropyl (2E,4E)-11methoxy-3,7,11-trimethyl-2-4 dodecadienoate, Isopropyl (2E,4E)-11methoxy-3,7,11-trimethyl-2-4 dodecadienoate (methoprene), Isopropyl (E,E)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate, Methopreen, Methopren, Methoprene, Methoprene (ANSI), Methoprene Isopropyl (WHO/FAO, 1984; PAN, 2005)
Chemical Group:	Not available (EXTOXNET, 1996)
Registered Trade Names:	Altosid, Altosid Bruquets, Altosid CP10, Altosid SR 10, Altosid IGR, Altosand, Apex, Diacon, Dianex, Extinguish, Fleatrol, Kabat, Manta, Minex, Ovitrol, Pharoid, Precor (EXTOXNET, 1996; U.S. EPA, 2001; WHO/FAO, 1984, n.d; PAN, 2005; HSDB, 2005)

USAGE

Methoprene is an insect growth regulator used indoors and outdoors to control a broad spectrum of insect pests in agricultural, horticultural, public health, and household applications. It is used on both food and nonfood crops, ornamentals, livestock, and mammalian pets (WHO/FAO, 1984; U.S. EPA, 2001, 2005; HSDB, 2005). Pest species it is used to control include mosquitoes, horn flies, beetles, tobacco moths, sciarid flies, fleas (eggs and larvae), fire ants, pharoah ants, midge flies, boll weevils, lice, leaf hoppers, plant hoppers, cucumber beetles, cigarette beetles, mites, Indian meal moths, and others. In public health applications, the most important uses are against flood water mosquitoes (U.S. EPA, 2001, 2005; WHO/FAO, n.d.). Slow-release formulations are applied to prevent the breeding of mosquitoes in places such as rice cultivations, storm drains, ponds, and water treatment works, among others (WHO/FAO, 1984). Because methoprene acts by disruption of insect development, it is not usually used for a quick kill in preharvest situations (WHO/FAO, 1984). Methoprene is used widely in the mushroom cultures to prevent the emergence of sciarid flies, it is mixed into feed supplements for cattle to control adult hornfly breeding in manure, and it is sprayed at food and tobacco handling and storage facilities (WHO/FAO, 1984; HSDB, 2005).

FORMULATIONS AND CONCENTRATIONS

Methoprene is available as technical grade product and in formulations including emulsifiable and soluble concentrates, suspension concentrates, granules, briquettes, aerosols, fogging solutions, baits, flowables, encapsulated and feed supplement formulations up to 10 percent ai (HSDB, 2005; EXTOXNET, 1996; WHO/FAO, 1984, n.d.). WHO indicated that the content of methoprene in the formulated products must be declared and shall not exceed the listed standards. Technical grade (RS)-methoprene must have no less than 920 g/kg (RS)-methoprene. The mean content of the highly active trans (E) isomer must be 900 g/kg while the maximum content of the cis (Z) isomer is 20 g/kg. For the (RS)-methoprene emulsifiable concentrate, the (RS)-methoprene content should be $\leq$ 25 g/kg + 15% of the declared content, > 25–100 g/kg + 10% of the declared content, 100–250 g/kg + 6% of the declared content (WHO, 2001).

SHELF LIFE

Methoprene is a stable compound (WHO/FAO, n.d.). It is stable in sterile aqueous solutions but biodegrades easily by common bacteria, sunlight, and ultraviolet light (WHO/FAO, 1984).

DEGRADATION PRODUCTS

Methoprene is rapidly and extensively degraded in the soil. The breakdown products include small amounts of nonpolar metabolites, including hydroxyl ester. However, more than 50 percent of the applied dose was

converted to carbon dioxide (WHO/FAO, 1984). In humans, methoprene is degraded and excreted in the urine as hydroxyepter (isopropyl 11-hydroxy-3,7,11-trimethyl - 2,4-dodecadienoate), the hydroxyacid (11-methoxy-3,7,11-trimethyl-2,4-dodecadienoic acid), and several lesser metabolites, including 7-methoxycitronellic acid, 7-hydroxycitronellic acid, and 7-methoxycitronellal which are excreted as free compound or conjugates (WHO/FAO, n.d.). Degradation products in unsterile pond water include ZR-724, ZR-725, ZR-669, and recovered methoprene each of which was a 1:1 mixture of cis-2 and trans-2 isomers, although 94 percent of the applied dose was trans-2 methoprene (WHO/FAO, 1984).

ENVIRONMENTAL BEHAVIOR

FATE AND TRANSPORT IN TERRESTRIAL SYSTEMS

Methoprene binds tightly to soil and it is only slightly soluble in water, making it almost immobile in most soil types (EXTOXNET, 1996; ATSDR, 2005). Field leaching studies in sand, sandy loam, silt loam and clay loam have shown that even after repeated washings with water, methoprene remains only in the top few inches of soil (EXTOXNET, 1996; WHO/FAO, 1984). In studies with radiolabeled methoprene, 87 percent of the applied dose was bound to the soil (WHO/FAO, 1984). These results indicate that methoprene does not leach from soil (U.S. EPA, 2001, 1991a, 1991b).

In soil, methoprene is of low persistence (EXTOXNET, 1996; U.S. EPA, 2001, 1991a, 1991b). It is rapidly and extensively broken down in soil (WHO/FAO, 1984). The reported field half-life is up to 10 days, while the half-life in sandy loam soil is about 10 days. The half-life of high application rates (1 pound/acre) of the formulated Altosid product is less than 10 days (EXTOXNET, 1996; ATSDR, 2005; WHO/FAO, n.d.). Methoprene is rapidly broken down by microbial degradation which is the major fate process to mostly carbon dioxide. It also undergoes rapid photodegradation (EXTOXNET, 1996; U.S. EPA, 2001, 1991a, 1991b; WHO/FAO, n.d.).

Additionally, formulated Altosid does not persist in plants. Half-lives of less than 1 day in rice, 2 days in alfalfa, and 3–7 weeks in wheat were reported. Methoprene residues are not expected in plants that are grown in treated soil (EXTOXNET, 1996; ATSDR, 2005).

FATE AND TRANSPORT IN AQUATIC SYSTEMS

Because methoprene binds tightly to soil and is practically insoluble in water, very little leaching into groundwater has been reported (EXTOXNET, 1996; ATSDR, 2005). Methoprene rapidly degrades in water. Half-lives in ponds have been reported at approximately 30 hours for application of 0.001 mg/L and 40 hours for application of 0.01 mg/L (EXTOXNET, 1996). Sunlight and temperature play major roles in the breakdown of methoprene in water (EXTOXNET, 1996; U.S. EPA, 2001; WHO/FAO, 1984). Half-lives of <1 day for sunlight conditions and > 4 weeks for darkness were reported (ATSDR, 2005). Biodegradation and photodegradation are the major fate processes (EXTOXNET, 1996). The potential for bioconcentration of methoprene in aquatic organisms is very high, as indicated by its bioconcentration factor of 3,400 (ATSDR, 2005).

HUMAN HEALTH EFFECTS

ACUTE EXPOSURE

Effects/Symptoms

There are limited data on the acute toxicity of methoprene in humans because no obvious signs of poisoning have been reported in humans from either accidental or occupational exposures (EXTOXNET, 1996; WHO/FAO, n.d.). In human health screening studies, no significant effects were seen (U.S. EPA, 1991a, 1991b). From those data and animal data it is concluded that methoprene has very low acute oral and

inhalation toxic potential in humans. It is also not a skin or eye irritant or a skin sensitizer in humans (U.S. EPA, 2001, 1991a, 1991b; WHO/FAO, n.d.).

In animals, acute oral and inhalation exposures to methoprene are almost nontoxic while dermal exposures are only slightly toxic (EXTOXNET, 1996; ATSDR, 2005). Oral LD_{50} values of 2,323 – >34,600 mg/kg in rats, 2,285 mg/kg in mice, and 5,000–10,000 mg/kg in dogs were reported. In rats, 20 percent mortality was seen within 4 months following oral doses of 232 mg/kg/day, while no deaths were seen at 116 mg/kg/day. In rats, an inhalation LC_{50} value of >210,000 mg/m^3 was reported, which was the highest dose tested. Reported dermal LD_{50} values range from > 2,000–10,000 mg/kg in rabbits and are > 5,000 mg/kg in rats (ATSDR, 2005; HSDB, 2005; EXTOXNET, 1996; WHO/FAO, n.d.; NIHE, 2001).

In short-term studies, no inhalation or dermal effects were reported in rats, rabbits, or dogs (U.S. EPA, 2001; WHO/FAO, n.d.; ATSDR, 2005). In subchronic studies, some systemic effects (e.g., increased liver weights and other liver and kidney effects in rats) have been observed at high concentrations (U.S. EPA, 2001, 1991a, 1991b; WHO/FAO, n.d.).

Methoprene is of low dermal toxicity. It does not cause skin or eye irritation in rabbits and it is not a skin sensitizer in guinea pigs (HSDB, 2005; EXTOXNET, 1996; ATSDR, 2005; U.S. EPA, 1991a, 1991b; WHO/FAO, n.d.; NIHE, 2001). No systemic effects were reported in rabbits dermally exposed in a 30-day study; erythema was reported at the application site (ATSDR, 2005; U.S. EPA, 2001). Additionally, hyperemia and edema of the skin was observed following repeated dermal applications (HSDB, 2005). Available data also suggest that methoprene is not genotoxic (NIHE, 2001).

Treatment

No laboratory tests have been identified as indicators of exposure to methoprene, and blood levels have not been established in humans (WHO, n.d.; HSDB, 2005). Because methoprene is of low acute toxicity, there are no clear signs or clinical symptom of toxicity in humans. If a person has been exposed to methoprene and shows signs of illness, treatment before being seen by a physician is supportive. Because no acute toxicity is expected even with ingestion of large doses, any illness seen following exposure is likely due to the solvent used in formulation (WHO/FAO, n.d.). Only following ingestion of large amounts of methoprene should gastrointestinal decontamination be employed. Recommended doses of activated charcoal include 25–100 g in adults and adolescents, 25–50 g in children, and 1 g/kg in infants less than one year old. Dermal exposure should be treated by decontamination of the skin by washing with soap and water. Treatment of ocular exposure consists of flushing the eyes with large amounts of saline or clean water. Medical attention should be sought if irritation continues (HSDB, 2005).

CHRONIC EXPOSURE

NONCANCER ENDPOINTS

Little data are available for humans following chronic exposures to methoprene, though it is not likely to cause long-term problems when used under normal conditions. No overt signs of toxicity have been reported from long-term occupational exposures (EXTOXNET, 1996). Based on animal studies, methoprene is not likely to cause chronic toxicity in human. Animal data indicate that the organ mainly affected by chronic methoprene exposure is the liver. Increased liver weights were reported in a 90-day feeding study in rats. However, these effects were not replicated in 2-year feeding studies in rats or in mice given methoprene in the diet for 90 days (EXTOXNET, 1996; U.S. EPA, 2001; WHO/FAO, n.d.).

Methoprene does not appear to have reproductive, developmental, or neurotoxic effects in animals. No reproductive effects were observed in a 3-generation reproduction study in rats or a 90-day study in dogs (EXTOXNET, 1996; ATSDR, 2005; U.S. EPA, 2001, 1991a, 1991b; WHO/FAO, n.d.; NIHE, 2001). No

teratogenic effects were seen in rats, rabbits, or mice (WHO/FAO, n.d.; EXTOXNET, 1996; ATSDR, 2005; U.S. EPA, 1991a, 1991b). Methoprene does not show potential estrogenic, androgenic anabolic, or glucocorticoid effects (U.S. EPA, 2001; WHO/FAO, n.d.).

CANCER ENDPOINTS

Existing data suggest that methoprene is not carcinogenic. Long-term feeding studies in rats and mice showed no increase in tumors (U.S. EPA, 1991a; EXTOXNET, 1996; NIHE, 2001). Additionally, methoprene does not show any mutagenic potential (EXTOXNET, 1996).

TOXICOKINETICS

Methoprene is absorbed via the gastrointestinal tract, inhalation of spray mist and through intact skin (WHO/FAO, n.d.). Oral absorption is rapid and extensive. It is distributed mainly to organs related to absorption, biotransformation, and excretion (NIHE, 2001). No evidence of accumulation in body tissues or fluids including fat, muscle, liver, lungs, blood, or bile was seen in a study using ^{14}C-labelled methoprene (WHO/FAO, 1984, n.d.). Methoprene is rapidly and completely metabolized and excreted in the urine, feces, and expired air of mammals (EXTOXNET, 1996; U.S. EPA, 2001; ATSDR, 2005; NIHE, 2001). In cattle, methoprene is excreted unchanged and in sufficient quantities in the feces to have the desired effect of killing larvae that breed in the waste (EXTOXNET, 1996). In mice intubated with radiolabeled methoprene, 63.6 percent and 12.3 percent of the radioactivity was excreted within 24 hours in the urine and feces, respectively (ATSDR, 2005).

The metabolism of methoprene occurs mainly by hepatocyte microsomal esterases to methoprene acid. After alpha oxidation, methoprene acid is susceptible to beta oxidation to acetate. It is then further broken down to carbon dioxide or intermediary metabolites by the Krebs' cycle. It is excreted from the body as carbon dioxide or in urine and feces. Poor intestinal absorption and rapid metabolism of absorbed methoprene may be indicated by the finding of high amounts of unmetabolized methoprene in the feces but not the urine or blood. Products of urinary excretion include the hydroxyepter (isopropyl 11-hydroxy-3,7,11-trimethyl - 2,4-dodecadienoate), the hydroxyacid (11-methoxy-3,7,11-trimethyl-2,4-dodecadienoic acid), and several lesser metabolites including 7-methoxycitronellic acid, 7-hydroxycitronellic acid, and 7-methoxycitronellal. Excretion of the primary urinary products is as free compounds or as conjugates. Methoprene is found in the eggs of laying hens and the milk of lactating cows (WHO/FAO, n.d.) however, no placental transfer was evident in mice (ATSDR, 2005). Approximately 8 percent of the radiolabel was excreted in the milk of lactating cows within 7 days while 19 percent was found in eggs of chickens after 14 days (NIHE, 2001). Most of the radiolabel in most species is excreted within 5 days (NIHE, 2001).

ECOLOGICAL EFFECTS

ACUTE EXPOSURE

Toxicity in Non-Targeted Terrestrial Organisms

Methoprene is very unlikely to harm terrestrial organisms other than its targets. It has a very low toxicity in birds (U.S. EPA, 2001, 1991a, 1991b; EXTOXNET, 1996; WHO/FAO, n.d.). Reported oral LD_{50} values include 4,640 ppm in chickens for the formulation Altosid and 2,000 mg/kg for mallard ducks (EXTOXNET, 1996). Reported acute 5–8 day LC_{50} values for Altosid in Mallard ducks and Bobwhite quail were all >10,000 ppm (EXTOXNET, 1996). Similar effects were reported in feeding studies using the technical material (WHO/FAO, n.d.). No reproductive effects or embryotoxicity were seen in mallard ducks and bobwhite quail fed Altosid (U.S. EPA, 2001, 1991a, 1991b; EXTOXNET, 1996; WHO/FAO, n.d.). However, acute oral exposure in birds to higher levels resulted in slowness, reluctance to move, sitting, withdrawal, and incoordination. These effects appeared quickly and persisted for up to 2 days making the birds potentially more susceptible to predation

(EXTOXNET, 1996). No toxicity was seen in honeybees or earthworms (EXTOXNET, 1996). The oral and dermal LD_{50} in bees is >1,000 µg/L/bee (HSDB, 2005). An unintended but beneficial effect has been observed in Japanese silk worms where exposure to methoprene extends the time period in which they make silk (WHO/FAO, n.d.).

Toxicity in Non-Targeted Aquatic Systems

Acute effects of methoprene have been reported in a wide variety of aquatic species. It is very highly toxic in aquatic insects, highly toxic in crustaceans, moderately toxic in zooplankton, and slightly toxic in molluscs and fish (PAN, 2005; EXTOXNET, 1996; U.S. EPA, 2001, 1991a, 1991b). In fish, accumulation, behavioral, biochemistry, growth, mortality, and population effects have been reported (PAN, 2005). In freshwater fish, methoprene is more toxic to warm-water fish and less toxic to cold-water fish (U.S. EPA, 1991a, 1991b). No death or toxicity was observed in mosquito fish treated for 10 weeks in ponds at 56–560 g/ha (WHO/FAO, n.d.). The reported 96-hour LC_{50}s in fish for the formulation Altosid range from 4.4 mg/L to > 100 mg/L in channel catfish and largemouth bass (EXTOXNET, 1996). For technical methoprene, reported LD_{50}s in fish range from 4,000 µg/L in Australian blue-eye to 124,950 µg/L in Mummichog (PAN, 2005).

Methoprene is highly acutely toxic to freshwater invertebrates such as crayfish and Daphnia manga (EXTOXNET, 1996; U.S. EPA 1991a, 1991b). Additionally, it can have high acute toxicity in estuarine and marine invertebrates such as grass shrimp and mud crabs; however, marine invertebrates are less likely to be exposed than estuarine invertebrates since methoprene is used as a mosquito larvicide. Additionally, the rapid degradation of methoprene in water mitigates the risks to estuarine organisms (U.S. EPA, 1991a, 1991b). In arthropods including crustacean, insecta, molluca, shrimp, damselfly, beetle, and tadpole, 24- and 48-hour LC_{50s} were greater than 900 ppb (U.S. EPA, 2001). The reported LC_{50} for freshwater shrimp is > 100 mg/L while it is > 0.1 mg/L for estuarine mud crab (EXTOXNET, 1996). Similar 5-day LC_{50} values for technical methoprene have been reported for crayfish, freshwater shrimp and white and pink shrimp (100 ppm) (WHO, n.d.). A 48-hour EC_{50} of 360 µg/L was reported for Daphnia (HSDB, 2005).

In amphibians, behavioral, developmental, growth, mortality, and population effects have been reported (PAN, 2005). The reported LC_{50} values for ***R. catesbeiana*** and ***R. pipiens*** larvae are greater than 10,000 ppb, and in adult ***B. woodhousei,*** the reported LC_{50} value is greater than the highest dose tested (>1,000 ppb) (U.S. EPA, 2001).

A slight potential for bioconcentration has been reported in bluegill sunfish and crayfish (EXTOXNET, 1996). Methoprene has an estimated bioconcentration factor of 3,400 which suggests that its potential for bioconcentration is very high (ATSDR, 2005).

CHRONIC EXPOSURE

Methoprene is of minimal chronic risk to freshwater fish, invertebrates, and other estuarine species from use in mosquito products (U.S. EPA, 2001). The use of briquettes poses a potential risk for chronic exposures in estuarine organism since methoprene is released slowly over an extended period of time (U.S. EPA, 1991a, 1991b). However, laboratory and field studies using mosquito product formulations have shown that methoprene dose not reach levels that are toxic to nontarget aquatic species during chronic exposures (U.S. EPA, 2001)

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PROFILE FOR NOVALURON

CAS REGISTRY NUMBER 116714-46-6

CHEMICAL SUMMARY

Novaluron (N-[[[3-chloro-4-[1,1,2-trifluoro-2-(trifluoromethoxy)ethoxy]phenyl]amino]carbonyl]-2,6-difluorobenzamide) is an insect-growth regulator (IGR) which inhibits chitin synthesis, thus affecting the molting stages of insect development. It acts by ingestion and contact and causes abnormal endocuticular deposition and abortive molting. It is used in agriculture/horticulture on a wide range of crops including cotton, soy, corn, fruit, potato and vegetables against a wide range of pests. Novaluron is recommended by the World Health Organization (WHO) as a mosquito larvicide (WHO 2011). Novaluron is being reviewed by EPA with regard to registration (Federal Register/Vol. 80, No. 60/Monday, March 30, 2015). At present, it is not considered a Restricted Use pesticide, due to low toxicity.

The most likely insect toxicity mode-of-action is that novaluron interrupts the *in vivo* synthesis and transport of specific proteins required for assemblage of polymeric chitin. As such, novaluron is of generally low acute, sub-acute and chronic toxicity. High doses can lead to erythrocyte damage and consequential effects on the spleen, together with some evidence of weight gain in mammalian species; although erythrocyte formation is not permanently affected and recovery appears to occur within weeks. Novaluron is of low toxicity to birds, fish, earthworms and aquatic plants; but is highly toxic to aquatic invertebrates (WHO 2004). There is no evidence for human carcinogenicity.

HUMAN HEALTH EFFECTS

DATA QUALITY AND QUANTITY

Novaluron has been studied and reviewed in terms of human toxicity. Key recent regulatory reports include the following:

- EPA 2011a. Novaluron: Pesticide Tolerances
- EPA 2011b. Novaluron: Human Health Risk Assessment for Proposed Section 3 Uses on Sweet Corn and in Food- or Feed-Handling Establishments
- EPA 2012. Registration of Novaluron for Indoor and Outdoor Use on Residential Sites
- WHO 2004. WHO Specifications and Evaluations for Public Health Pesticides: Novaluron
- WHO 2011. Guidelines for Drinking-Water Quality

Novaluron is also listed in EPA's Human Health Benchmarks for Pesticides database (https://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home).

TOXICITY

WHO has established a chronic ADI of 0 to 0.01 mg/kg on the basis of a NOAEL of 1.1 mg/kg body weight per day for erythrocyte damage and secondary splenic and liver changes in a 2-year dietary study in rats, using a safety factor of 100 (WHO 2004, 2011). Acute values were not established, due to low toxicity. It was not considered appropriate to set a formal guideline value for novaluron as a vector control agent in drinking-water. For example, at the maximum recommended dosage for drinking-water of 0.05 mg/l, the intake of a 60 kg adult drinking 2 litres of water would represent only 17% of the upper limit of the ADI.

EPA did not estimate acute reference doses (RfDs), noting that "an endpoint of concern attributable to a single dose was not identified" (EPA 2011a). EPA used the same dietary study in rats as WHO to estimate chronic oral and intermediate inhalation RfDs. EPA derived a chronic dietary Population Adjusted Dose (PAD; equivalent in this case to an RfD), based upon a NOAEL of 1.1 mg/kg/d and endpoints of

erythrocyte damage and regenerative anemia. A 100 fold uncertainty factor was applied (10 for interspecies, and 10 for intraspecies) to result in a PAD/RfD of 0.011 mg/kg/d. EPA derived intermediate dermal and acute inhalation NOEALs from a 90-day feeding study in rats, with decreased hemoglobin, hematocrit, and red-blood cell counts; plus histopathology (increased hematopoieses and hemosiderosis in spleen and liver). A NOAEL of 4.38 mg/kg/d was determined, and a "level of concern" (LOC) for margin of exposure (MOE was determined as "<100". Applying the LOC in a similar fashion as an uncertainty factor results in an RfD of 0.044. EPA (2011a) suggests a dermal absorption factor of 100%, but EPA (2011b) suggests 10%.

HUMAN TOXICITY BENCHMARK SUMMARY

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Chronic	Oral	0.011	mg/kg/d	RfD, NOAEL of 1.1 mg/kg/d based on erythrocyte damage and anemia in chronic feeding study in rats. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations.)	EPA 2016
Chronic	Oral	77	ppb	HHBP	EPA 2016
Chronic	Oral	0.011	mg/kg/d	NOAEL of 1.1 mg/kg/d based on erythrocyte damage and anemia in chronic feeding study in rats. A UF of 100 was applied by EPA to derive the RfD (10x interspecies variability, 10x sensitive human subpopulations.)	EPA 2011a, b
Intermediate	Dermal	0.044 or 0.0044	mg/kg/d	NOAEL of 4.38 mg/kg/d based on hematological effects in a 90-day feeding study in rats. MOE of <100; applied as a UF of 100. A 100% absorption factor is suggested for application in risk assessment in EPA 2011a, but EPA 2011b suggests 10%.	EPA 2011a, b
Acute	Inhalation	0.044	mg/kg/d	NOAEL of 4.38 mg/kg/d based on hematological effects in a 90-day feeding study in rats. MOE of <100; applied as a UF of 100.	EPA 2011a
Intermediate	Inhalation	0.011	mg/kg/d	NOAEL of 1.1 mg/kg/d based on erythrocyte damage and anemia in chronic feeding study in rats. MOE of <100; applied as a UF of 100.	EPA 2011a

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Chronic	Oral	0.01	mg/kg/d	NOAEL of 1.1 mg/kg body weight per day for erythrocyte damage and secondary splenic and liver changes in a 2-year dietary study in rats, using a safety factor of 100	WHO 2004, 2011

Abbreviations: ADI= acceptable daily intake, HHBP= human health benchmark for pesticides (in water), LOC= level of concern, MOE= margin of exposure, NOAEL= no observed adverse effect level, RfD= reference dose, UF=uncertainty factor

ECOLOGICAL EFFECTS

DATA QUALITY AND QUANTITY

EPA is currently conducting Biological Evaluations (BEs) for assessing risks to threatened and endangered species from selected pesticides. These BEs include many types of terrestrial, aquatic (both freshwater and marine), and avian animal species; as well as plants. At this time, a BE for novaluron does not appear to be available. There do not appear to be comprehensive regulatory reviews of novaluron's ecological effects, likely because of its limited toxicity compared to other pesticides.

ENVIRONMENTAL BEHAVIOR

Novaluron's use will result in its direct release to the environment. Novaluron is slightly persistent in soil and sediments. Neither novaluron nor its major breakdown products are mobile in soil and, therefore, are not expected to leach into groundwater. Based on its low volatility (vapor pressure and Henry's law constant), novaluron residues are not expected in the air. Novaluron is stable to hydrolysis at pHs 5 and 7. At pH 9, extrapolated half-lives were 87.7 and 113.6 d. Novaluron hydrolysis is temperature dependent, with half-lives of 1.2 days and 8.5 hours at 50 deg C and 70 deg C, respectively. Photolysis half-lives in water were found to be 173.3 and 119.5. In soil, phtolysis half-lives were found to be 231.1 and 288.8 d. Novaluron had a half-life of 10-91 d in soil (Health Canada 2006)

A log K_{ow} of 4.3 indicates the potential for novaluron bioaccumulation, which is supported by two bioconcentration studies. In these studies, novaluron was readily accumulated by fish during exposure. Novaluron steady state concentrations were attained within 21-35 d, with bioconcentration factors (BCFs) of 14220-14645 for the whole body. Approximately 40 days were required for 95% novaluron depuration from the whole body. The relatively high level of novaluron bioconcentration by fish, its resistance to significant transformation and its slow rate of loss during depuration suggest that it may have some potential for persistence in the aquatic food chain, particularly when frequent applications are made (Helath Canada 2006).

TOXICITY

Novaluron has been studied and reviewed in terms of aquatic toxicity under the Clean Water Act. The following values are from the EPA Office of Pesticide Programs database (at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/aquatic-life-benchmarks-pesticide-registration).

ECOLOGICAL TOXICITY BENCHMARK SUMMARY

Duration	Species	Value	Units	Endpoint
Acute	Fish	490	ug/L	Toxicity value x LOC. For acute fish, toxicity value is generally the lowest 96-hour LC50 in a standardized test (usually with rainbow trout, fathead minnow, or bluegill), and the LOC is 0.5.
Chronic	Fish	6.16	ug/L	Toxicity value x LOC. For chronic fish, toxicity value is usually the lowest NOEAC from a life-cycle or early life stage test (usually with rainbow trout or fathead minnow), and the LOC is 1.
Acute	Invertebrates	0.075	ug/L	Toxicity value x LOC. For acute invertebrate, toxicity value is usually the lowest 48- or 96-hour EC50 or LC50 in a standardized test (usually with midge, scud, or daphnids), and the LOC is 0.5.
Chronic	Invertebrate	0.03	ug/L	Toxicity value x LOC. For chronic invertebrates, toxicity value is usually the lowest NOAEC from a life-cycle test with invertebrates (usually with midge, scud, or daphnids), and the LOC is 1.
Acute	Nonvascular Plants	3549	ug/L	Toxicity value x LOC. For acute nonvascular plants, toxicity value is usually a short-term (less than 10 days) EC50 (usually with green algae or diatoms), and the LOC is 1.
Acute	Vascular Plants	75.4	ug/L	Toxicity value x LOC. For acute vascular plants, toxicity value is usually a short-term (less than 10 days) EC50 (usually with duckweed) and the LOC is 1.

Notes:

Values from https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/aquatic-life-benchmarks-pesticide-registration

Abbreviations: EC_{50}= 50% effect concentration, LC_{50}= 50% lethal concentration, LOC=level of concern, n/a= not available, NOAEC=no observed adverse effect concentration

The ecological data annex (D-4) contains further information on ecological toxicity values.

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WHO 2011. Guidelines for Drinking-Water Quality. Fourth Edition. World Health Organization, Geneva, Switzerland.

PROFILE FOR PERMETHRIN:

CAS REGISTRY NUMBER 52645-53-1

SUMMARY

CHEMICAL HISTORY

Permethrin is a synthetic pyrethroid insecticide used in agricultural and human health applications. It is similar to the natural insecticide pyrethrum, which comes from chrysanthemums; however, it is more effective and longer lasting (WHO/FAO, 1984; IPCS, 1990). For mosquito control, it is used in bed nets and other materials that are dipped in permethrin to protect the user (EXTOXNET, 1996; WHO/FAO, 1984). Permethrin is of low risk to humans when used at levels recommended for its designed purpose (ATSDR, 2003a). However, as a synthetic pyrethroid, permethrin exhibits its toxic effects by interfering with the way the nerves and brain normally function. Typical symptoms of acute exposure are irritation of skin and eyes, headaches, dizziness, nausea, vomiting, diarrhea, and excessive salivation and fatigue. Inhaled permethrin has been shown to cause cutaneous paresthesias or a burning, tingling, or stinging. However, these effects are generally reversible and disappear within a day of removal from exposure (ATSDR, 2003a).

DESCRIPTION OF DATA QUALITY AND QUANTITY

Several comprehensive reviews on the toxicity of permethrin have been prepared or updated in recent years:

- Toxicological Profile for Pyrethrin and Pyrethroids (ATSDR, 2003a)
- An EPA risk assessment for the Reregistration Eligibility Decision (RED) document (U.S. EPA, 2005f)
- IRIS summary review (U.S. EPA, 2005g).

EPA and ATSDR have developed quantitative oral human health benchmarks (EPA's acute and chronic RfDs, short-, intermediate-, and long-term inhalation and dermal benchmarks and ATSDR's acute and intermediate oral MRLs). Other relevant references include

- Environmental Health Criteria 94: Permethrin (IPCS, 1990)
- Specifications for Permethrin (WHO, 1999a).

SUMMARY TABLE

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute, Intermediate, Chronic	Inhalation	0.11	mg/kg/day	Inhalation NOAEL of 0.042 mg/L (11 mg/kg/day) for neurological effects in rats with UF of 100 applied	U.S. EPA (2005f)
Acute, Intermediate, Chronic	Oral	0.25	mg/kg/day	Acute and chronic RfD based on clinical effects in rats	U.S. EPA (2005f)
Acute, Intermediate, Chronic	Dermal	5	mg/kg/day	Dermal NOAEL of 500 mg/kg/day in rats with a UF of 100 applied	U.S. EPA (2005f)

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Cancer	Inhalation, Oral, Dermal	0.009567	per mg/kg/day	CSF for lung tumors in female mice	U.S. EPA (2005f)

For inhalation exposure, a NOAEL of 0.042 mg/L (11 mg/kg/day) was identified for neurological effects in rats exposed via inhalation and an uncertainty factor of 100 was applied. This value is appropriate for short- (1–30 days), intermediate- (1–6 months), and long-term (>6 months) inhalation exposures (U.S. EPA, 2005f).

For oral exposure, an acute and chronic oral RfD of 0.25 mg/kg/day was derived based on a NOAEL of 25 mg/kg/day for clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature observed in rats, with an uncertainty factor of 100 applied (U.S. EPA, 2005f). The acute and chronic RfD was adopted to also represent intermediate exposures.

For dermal exposure, a NOAEL of 500 mg/kg/day was identified in rats dermally exposed for 21 days and an uncertainty factor of 100 was applied. This value is appropriate for all exposure durations (U.S. EPA, 2005f).

To assess potential carcinogenic risks, a cancer slope factor (CSF) of 9.567×10^{-3} per mg/kg/day was derived based on lung tumors in female mice chronically exposed to permethrin in the diet (U.S. EPA, 2005f).

INSECTICIDE BACKGROUND

CASRN:	52645-53-1
Synonyms:	3-Phenoxyphenyl)methyl3-(2,2-dichloroehenyl)-2,2-dimethylcyclopropanecarboxylate (ATSDR, 2003a)
Chemical Group:	pyrethroid
Registered Trade Names:	Ambush, BW-21-Z, Cellutec, Dragnet, Ectiban, Eksmin, Exmin, FMC 33297, Indothrin, Kafil, Kestrel, NRDC 143, Pounce, PP 557, Pramex, Qamlin, and Torpedo (EXTOXNET, 1996), Acion, AI3, AMbushfog, BW-21-7, CO-Opex, Matadon, NIA 33297, Outflank, OMS-1821, Perthrine, Picket G, Perigen, PP557, R86557, Stockade, Stomoxin, S-3151, SBP-1513, Talcord, WL43479 (WHO/FAO, 1984)

USAGE

Permethrin is used as a broad spectrum insecticide to combat pests on a variety of crops. It is also used to control ectoparasites in animals, biting flies, and cockroaches and is used in greenhouses, gardens, and for termite control (EXTOXNET, 1996). It belongs to the pyrethroid class of insecticides, which have long been used to control mosquitoes, human lice, beetles, and flies (ATSDR, 2003a). For mosquito protection, it is used in bed nets and other materials that are dipped into the permethrin to protect the user. Permethrin for agricultural use is restricted by EPA due to its potential toxicity to aquatic organisms, and it may only be purchased and used by certified applicators (ATSDR, 2003a).

FORMULATIONS AND CONCENTRATIONS

Permethrin is available in technical grade, emulsifiable concentrates, dusts, smokes, ultra-low volume (UVL), and wettable powder formulations (EXTOXNET, 1996). Technical grade permethrin may be mixed with carriers or solvents resulting in the commercial formulations. These commercial formulations may also include ingredients that may potentiate the toxicity compared to technical grade permethrin. These ingredients must be identified on the label. WHO indicated that the content of permethrin in the formulated products must be declared and shall not exceed the listed standards. For impregnated mosquito netting, the permissible permethrin content is 20 +/- 3 mg/kg (WHO, 2002). Technical grade permethrin must have no less than 900 g/kg permethrin. The emulsifiable concentrate should contain > 25–100 g/kg +/- 10% of the declared content, 100–250 g/kg +/- 6% of the declared content, or > 250–500 g/kg +/- 5% of the declared content (WHO, 1999a). Permethrin that is used for bed nets comes in the emulsifiable concentrations ranging from 10 to 55 percent active ingredient. The 55 percent emulsifiable concentration is only for professional use (WHO, 1999a).

SHELF LIFE

Permethrin is stable for 2 years or longer at 50°C. It is most stable in acidic environments and optimal stability is at pH 4. Photochemical degradation occurs in laboratory studies but not in field data. Pyrethrins, in general, are stable for a long time in water-based aerosols (HSDB, 2005).

DEGRADATION PRODUCTS

Pyrethroid insecticides are often formulated with synergists that act to prevent the breakdown of enzymes and thus enhance the activity of the pyrethroid (ATSDR, 2003a). Permethrin needs to be stored in a dry, cool, well-ventilated location to prevent the risk of it breaking down prior to use. Permethrin's breakdown products include 3-phenoxybenzyl(1RS)-cis, trans-3-(2,2-dichloroviny)-2-2dimethylcyclopropanecarboxylate (PAN, 2005).

ENVIRONMENTAL BEHAVIOR

FATE AND TRANSPORT IN TERRESTRIAL SYSTEMS

Permethrin is moderately stable in the environment (WHO/FAO, 1984). It binds tightly to soil making it almost immobile in most soil types. Studies have shown that permethrin is immobile in clay and loamy sands, while its degradation products have some mobility. As a result, it is not easily taken up by plants or leached into groundwater (ATSDR, 2003a).

In soil, permethrin is of low to moderate persistence (EXTOXNET, 1996). The reported half-life ranges from 30 to 38 days in soil (EXTOXNET, 1996) and < 2.5 days in a sediment and seawater solution. The U.S. Department of Agriculture (USDA) Pesticide Database lists the half-life of permethrin as 4–40 days in aerobic soils. It is broken down largely by microorganisms in nonsterile soil and may also be broken down by sunlight at the surface of soil (ATSDR, 2003a).

FATE AND TRANSPORT IN AQUATIC SYSTEMS

Permethrin is not expected to be released in large quantities into water because it is generally applied to crops and vegetation aerially or on the ground from sprayers. Nearby waters, however, might be affected by spray drift. Permethrin is prohibited from being applied for mosquito control within 100 feet of lakes, rivers, or streams due to its aquatic toxicity (ATSDR, 2003a). Because permethrin binds tightly to soil and is practically insoluble in water, very little leaching into groundwater has been reported (EXTOXNET, 1996). Due to its low vapor pressure and Henry's law constant, permethrin volatilizes slowly from water. When permethrin is

released into water, it rapidly partitions to suspended solids and sediments, which further mitigates volatilization. Studies have shown that greater than 95 percent of permethrin applied directly onto lake sediment was absorbed.

Permethrin breaks down quickly in water. Studies have reported a half-life of < 2.5 days near estuarine areas (EXTOXNET, 1996). Additionally, permethrin undergoes photolysis in sunlit surface waters, with a reported half-life of 14 days in seawater exposed to light (ATSDR, 2003a). In water, a loss of toxicity was observed for permethrin that had aged for 48 hours in sunlight (EXTOXNET, 1996).

HUMAN HEALTH EFFECTS

ACUTE EXPOSURE

Effects/Symptoms

There are limited data on the acute toxicity of permethrin in humans. Acute effects observed from occupational exposure include burning and itching of the skin of the periorbital area within a few hours of inhalation exposure to permethrin. Ingestion of permethrin causes nausea and vomiting. As a Type I pyrethroid, its primary target is the nervous system (U.S. EPA, 2005f). Typical effects seen following acute exposure to higher levels of permethrin are almost all related to the action of it on the nervous system, as pyrethroids prolong the open phase of the sodium channel during nerve cell excitation. Animal studies have indicated that effects may be caused by repetitive activity in sensory motor nerves (IPCS, 1990; WHO/FAO, 1984). These symptoms of permethrin exposure are transitory and disappear anywhere within a few hours to a few of days once the exposure is discontinued (EXTOXNET, 1996).

In animals, oral and inhalation exposures to permethrin are almost nontoxic. Reported LD_{50} values for technical permethrin range from 430 to 4,000 mg/kg in rats, while a 4-hour LC_{50} of 23.5 mg/L is reported in rats. Permethrin is slightly toxic through dermal contact, with dermal LD_{50}s of over 4,000 mg/kg in rats and over 2,000 mg/kg in rabbits. The toxicity depends on the ratio of cis and trans isomers, with cis being more toxic, and the solvent used (EXTOXNET, 1996; WHO/FAO, 1984). Reported dermal LD_{50} values include > 4,000 mg/kg (no solvent) in rabbits, > 2,500 mg/kg (no solvent) in rats and mice, and 750 mg/kg (in xylene) in rats (WHO/FAO, 1984). Dermal exposure to permethrin has caused mild irritation to both intact and abraded skin of rabbits (EXTOXNET, 1996).

Treatment

Permethrin and its metabolites can be detected in blood and urine; however the methods are not practical given how quickly these compounds are broken down in the body (ATSDR, 2003a; WHO/FAO, 1984). Levels of the degradation product 3-phenoxybenzyl in urine may be useful indicators of exposure (WHO/FAO, 1984).

There are no antidotes for permethrin exposure. Treatment depends on the symptoms of the exposed person. If a person exhibits signs of typical pyrethroid toxicity following permethrin exposure (nausea, vomiting, shortness of breath, tremors, hypersensitivity, weakness, burning, or itching), they should immediately remove any contaminated clothing. Any liquid contaminant on the skin should be soaked up and the affected skin areas cleaned with alkaline soap and warm water. Eye exposures should be treated by rinsing with copious amounts of 4 percent sodium bicarbonate or water. Contact lenses should be removed. Vomiting should not be induced following ingestion exposures, but the mouth should be rinsed. The person should be kept calm and medical attention should be sought as quickly as possible (PAN, 2005; WHO/FAO, 1984). Medical personnel will treat severe intoxications with a sedative and anticonvulsant. Ingestion of large amounts of permethrin should be treated with gastric lavage using a 5 percent bicarbonate solution followed

by powdered activated charcoal. Skin irritation may be treated with a soothing agent and exposure to light should be avoided.

CHRONIC EXPOSURE

NONCANCER ENDPOINTS

Little data are available for humans following chronic exposures to permethrin, though it is not likely to cause long-term problems when used under normal conditions (EXTOXNET, 1996). Chronic occupational exposure to permethrin caused skin and eye irritation in 33 percent of exposed Swedish workers. However, no complaints were reported in volunteers exposed to 0.5 mg/m^3 from an indoor application (WHO/FAO, 1984).

Data in animals indicate that oral exposure to permethrin is not highly toxic, but effects reported are largely neurological. Doses of 5 mg/kg/day for 90 days did not produce effects in dogs (EXTOXNET, 1996) while higher oral doses of 500 mg/kg and greater for 3 months caused transient clinical signs. Mice and rats chronically exposed to dietary levels up to 5,000 mg/kg (mice) and 2,500 mg/kg (rats) exhibited no consistent effects on growth or food consumption (WHO/FAO, 1984). Inhalation and dermal studies in animals indicate that permethrin is nontoxic or minimally toxic. No effects were observed in rats exposed to up to 500 mg/m^3, 6 hours per day, for 13 weeks. Additionally, rabbits dermally exposed to 1.0 g/kg/day on abraded skin for 21 days showed no effects other than moderate skin irritation (WHO/FAO, 1984). Based on the lack of reproductive effects in animals exposed to high oral does of permethrin, human reproductive toxicity is not expected. Additionally, permethrin shows no teratogenic or mutagenic activity (EXTOXNET, 1996; WHO/FAO, 1984).

CANCER ENDPOINTS

EPA has classified permethrin as "likely to be carcinogenic to humans" by the oral route. A long-term, high dose dietary exposure study reported an increased incidence of benign lung and liver tumors in mice. This is supported by equivocal evidence in one strain of rats and structure-activity relationship information (U.S. EPA, 2005f).

TOXICOKINETICS

Permethrin is readily absorbed via the gastrointestinal tract, inhalation, and less so through intact skin (WHO/FAO, 1984). In mammals, permethrin is rapidly metabolized in the liver (EXTOXNET, 1996). The trans isomer is metabolized by hydrolysis and the cis isomer is not as easily hydrolyzed and is thus more toxic (WHO/FAO, 1984). The hydroysis and oxidation products of permethrin metabolism are quickly excreted in urine and feces with the trans isomers more rapidly excreted than the cis isomers. The primary excretion products of both isomers in most species studied include 4'-HO-3-PBA sulfate (in rats), 4'-HO-3-PBA (trans) and 6-HO-3-PBA (cis) sulfates (in mice), N-(3-phenoxybenzoyl) glutamate (in cows), and cyclopropane-carboxylic acid glucuronides and 3-PBA glucuronides products in most of the species studied (WHO/FAO, 1984). Permethrin may persist in fatty tissues. The reported half-life in the brain and body fat is 4–5 days (EXTOXNET, 1996).

ECOLOGICAL EFFECTS

ACUTE EXPOSURE

Toxicity in Non-Targeted Terrestrial Organisms

Permethrin, like other pyrethroids, is very unlikely to harm terrestrial organisms other than its targets, such as mosquitoes and other pests (EXTOXNET, 1996). Permethrin has a very low toxicity in birds (WHO/FAO,

1984; EXTOXNET, 1996). Oral LD_{50} values range from 9,900 mg/kg for the formulation Pramex in mallard ducks to over 15,500 mg/kg in Japanese quail (EXTOXNET, 1996), while the acute oral LD_{50} for the technical material was >11,275 mg/kg in mallard ducks and >32,000 mg/kg in starlings. Subacute LD_{50}s were >23,000 mg/kg for all bird species tested. No adverse effects or significant accumulation in tissues or eggs were seen in hens exposed to a spray mist of 3.77–11.94 mg/bird (WHO/FAO, 1984). As with other pyrethroid insecticides, permethrin is extremely toxic to honey bees (EXTOXNET, 1996).

Toxicity in Non-Targeted Aquatic Systems

Permethrin is very toxic to fish (EXTOXNET, 1996); however, because it is rapidly absorbed and degraded in the aquatic environment, the risk is of short duration (WHO/FAO, 1984). The high toxicity in fish is illustrated by the low exposures that cause lethality. The reported 48-hour LC_{50} for rainbow trout is 0.0054 mg/L, while in bluegill sunfish and salmon it is 0.0018 mg/L (EXTOXNET, 1996). The 96-hour LC_{50}s range from 0.1–0.5 µg/L in rainbow trout to 15 µg/L in mosquito fish (WHO/FAO, 1984). Permethrin has a low to moderate potential to accumulate in fish, with reported bioconcentration factors of over 700 times the concentrations in water for bluefish and catfish (EXTOXNET, 1996). A bioconcentration factor of 1,900 was reported in eastern oysters following a 28-day incubation (ATSDR, 2003a). Permethrin is also known to be toxic to some aquatic invertebrates, amphibians in larval form, aquatic insects, and crustaceans (WHO/FAO, 1984). A disruption in growth and development of tadpoles has been reported (EXTOXNET, 1996).

CHRONIC EXPOSURE

Due to low rate of application and low persistence of permethrin in both terrestrial and aquatic environments, serious adverse effects are not anticipated from chronic exposures (HSDB, 2005)

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PROFILE FOR PIRIMIPHOS-METHYL:

CAS REGISTRY NUMBER 29232-93-7

SUMMARY OF INSECTICIDE

CHEMICAL HISTORY

Pirimiphos-methyl is a fast-acting, broad spectrum, noncumulating organophosphate insecticide and acaricide used in agricultural, horticultural, and public health applications (WHO/FAO, 1983, 1974). In public health applications, it is used to control disease vector insects, including mosquitoes, ants, beetles, bed-bugs, cockroaches, fleas, flies, lice, and mites (WHO/FAO, 1983, 1974). Pirimiphos-methyl has both contact and fumigant action (WHO/FAO, 1974). It is applied as a liquid concentrate, ready to use formula, and as treated articles (ear tags) (U.S. EPA, 1999b). It can be applied by closed system containers, low- and high-pressure hand wands, backpack sprayers, tagging equipment, and foggers (U.S. EPA, 2001). Pirimiphos-methyl acts like other organophosphates by inhibiting cholinesterase activity (U.S. EPA, 1999d). It is of low mammalian toxicity (WHO/FAO, 1983). WHO/FAO (1992) has classified it as slightly hazardous. Early symptoms of pirimiphos-methyl exposure include excessive sweating, headache, weakness, giddiness, nausea, vomiting, stomach pains, blurred vision, slurred speech, and muscle twitching. Symptoms of more severe poisoning may advance to convulsions, coma, loss of reflexes, and loss of sphincter control (WHO/FAO, 1983).

DESCRIPTION OF DATA QUALITY AND QUANTITY

Comprehensive reviews on the toxicity of pirimiphos-methyl have been prepared:

- Interim Reregistration Eligibility Decision for Pirimiphos-methyl Case No. (2535) (U.S. EPA, 2001)
- IRIS summary review (U.S. EPA, 2006)
- Data Sheet on Pesticide No. 49 – Pirimiphos-methyl (WHO/FAO, 1983).

EPA has developed quantitative human health benchmarks that include an oral acute and chronic RfD and short- and intermediate-term inhalation and dermal benchmarks.

SUMMARY TABLE

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute	Inhalation	0.015	mg/kg/day	Oral LOAEL for neurological effects in rats with UF of 1000 applied; assume no portal of entry effects	U.S. EPA (2001)
Intermediate	Inhalation	0.0007	mg/kg/day	Oral LOAEL for neurological effects in rats with UF of 300 applied; assume no portal of entry effects	U.S. EPA (2001)
Chronic	Inhalation	0.0007	mg/kg/day	Adopt intermediate for chronic duration	U.S. EPA (2001)

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute	Oral	0.015	mg/kg/day	Acute oral RfD based on a LOAEL of 15 mg/kg/day for neurological effects in rats and UF of 1,000 applied	U.S. EPA (2001)
Intermediate	Oral	0.0002	mg/kg/day	Adopt chronic RfD for intermediate duration	U.S. EPA (2001)
Chronic	Oral	0.0002	mg/kg/day	Chronic oral RfD based on a LOAEL of 0.2 mg/kg/day for neurological effects in rats and UF of 1,000 applied	U.S. EPA (2001)
Acute	Dermal	0.015	mg/kg/day	Oral LOAEL for neurological effects in rats with UF of 1,000 applied; assume no first pass effects and 100% oral absorption	U.S. EPA (2001)
Intermediate	Dermal	0.0007	mg/kg/day	Oral LOAEL for neurological effects in rats with UF of 300 applied; assume no first pass effects and 100% oral absorption	U.S. EPA (2001)
Chronic	Dermal	0.0007	mg/kg/day	Adopt intermediate for chronic duration	

For oral exposure, an acute RfD of 0.015 mg/kg/day was derived based on a LOAEL of 15 mg/kg/day for brain, red blood cell, and plasma cholinesterase inhibition in rats (EPA MRID# 43594101, citation not provided). An uncertainty factor of 1,000 was applied for the use of a LOAEL and the degree of cholinesterase inhibition (10), and intra- and inter-species variability (100) (U.S. EPA, 2001).

A chronic oral RfD of 0.0002 mg/kg/day was derived based on an LOAEL of 0.2 mg/kg/day for plasma cholinesterase inhibition in a subchronic rat study (EPA MRID# 43608201, citation not provided). An uncertainty factor of 1,000 was applied for the use of a LOAEL and data gaps for long-term studies (10), and intra- and inter-species variability (100) (U.S. EPA, 2001). The chronic RfD was used to represent intermediate exposures.

For inhalation and dermal exposure, the oral toxicity endpoints (i.e., LOAELs) were selected for use, and both assume 100 percent absorption and no first pass or portal-of-entry effects (U.S. EPA, 2001). For acute inhalation and dermal benchmarks, an uncertainty factor of 1,000 was applied for the use of a LOAEL and the degree of cholinesterase inhibition (10), and intra- and inter-species variability (100). For intermediate inhalation and dermal benchmarks, an uncertainty factor of 300 was applied for the use of a LOAEL (3) and intra- and inter-species variability (100). The intermediate benchmark was used to represent chronic exposures.

INSECTICIDE BACKGROUND

CASRN:	29232-93-7
Synonyms:	O-(2-Diethylamino)-6-methyl-4-pyrimidinyl) O,O-dimethyl phosphorothioate, 2-diethylamino-6-methylpyrimidin-4-yl dimethyl phosphorothionate, pirimifosmethyl, methylpirimiphos, pyridimine

	phosphate, ENT 27699GC, PP511, CMS 1424 (U.S. EPA, 2001, 2006; WHO/FAO, 1983
Chemical Group:	organophosphate (U.S. EPA, 2001; WHO/FAO, 1983)
Registered Trade Names:	Actellic 5E, Atelic, Atellic, Atellifog, Blex, Nu-Gro Insecticide, Nu-Gro 5E, Tomahawk Insecticide Ear Tags, LPM Insecticide Ear Tags, Silosan, Sybol (U.S. EPA, 2001, 2006; WHO/FAO, 1983)

USAGE

Pirimiphos-methyl is a fast-acting, broad spectrum organophosphate insecticide and acaricide used to control a wide variety of sucking and chewing pests in agricultural and horticultural applications. It is used in horticultural applications; to clean fruits and vegetables before harvest; to control pests on stored products; and to eradicate nuisance and disease vector insects, including mosquitoes, ants, beetles, bed-bugs, cockroaches, fleas, flies, lice, and mites (WHO/FAO, 1983, 1974). The intended uses of existing products include greenhouse applications, treatment of stored grain and seeds (corn and sorghum) intended for both human and animal consumption, and direct animal applications including incorporation into cattle eartags and sprays (U.S. EPA, 1999c, n.d.). Pirimiphos-methyl is used to control a large number of different insects including, but not limited to, cigarette beetles; confused flour beetles; corn sap beetles; flat grain beetles; hairy fungus beetles; red flour beetles; sawtoothed beetles; granary weevils; maize weevils; merchant grain beetles; rice weevils; lesser grain borers; and angoumois grain moths, Indian meal moths, and almond moths on corn (seed and whole-grain), rice (whole-grain), wheat (whole-grain), and grain sorghum (seed and whole-grain); mealy bugs; mites (iris bulbs) horn flies and face flies (U.S. EPA, 2001). For malaria control, typical use includes the application of 1 or 2 g pirimiphos-methyl/m^3 of a 2–5 percent suspension to indoor walls and ceilings every 3 months. Ultra-low-volume (ULV) sprays and thermal fogs are additional application methods. To control DDT resistant fleas, a 2 percent dust is applied in rodent burrows. Pirimiphos-methyl is not recommended for use directly on humans or on processed foods (WHO/FAO, 1983; U.S. EPA, 1999c). Current registered uses in the United States include food and non-food uses. Food uses include use on sorghum, corn (gain and seed), nonlactating dairy cattle, beef/range/feeder cattle, and calves. Non-food uses include use on iris bulbs. No residential or public health uses are currently registered in the United States (U.S. EPA, 2001)

FORMULATIONS AND CONCENTRATIONS

There are several typical formulations for pirimiphos-methyl, each formulation varying in the amount of active ingredient (ai) it contains. The typical formulations for pirimiphos-methyl include (U.S. EPA, 1999c, 2001; WHO/FAO, 1983) the following:

- U.S. registered formulations: emulsifiable liquid concentrate (57 percent ai), treated ear tags (14 percent and 20 percent ai)
- For agricultural and horticultural uses: emulsifiable concentrate (250–500 g ai/L), ULV concentrate (500 g ai/L), encapsulated formulas (250–400 g ai/kg), dusts (10 and 20 g ai/kg), wettable powders (250 and 400 g ai/kg), fog (100 g ai/L), aerosol (20 g ai/L with pyrethroids), solvent free formulation (900 g ai/kg), smoke generator formulation
- For public health uses: emulsifiable concentrate (250 and 500 g ai/L), ULV concentrate (500 g ai/L), encapsulated formulation (200 g ai/L), dusts (10 and 20 g ai/kg), wettable powder (250 and 400 g ai/kg), fog (100 g ai/L), aerosol (20 g ai/L with pyrethroids), solvent-free formulation (900 g ai/kg), smoke generator formulation

- For household uses: emulsifiable concentrate (80 g ai/L), dusts and aerosols (with pyrethroids) for use in the home and garden.

DEGRADATION PRODUCTS

Stored pirimiphos-methyl products are broken down by hydrolysis of the phosphorus-ester side chain, which results primarily in the parent hydroxyl-pyrimidine (WHO/FAO, 1974). The main hydrolysis degradates at pH 5, 7, and 9 were 2 (diethylamino)-4-hydroxy-6-methyl pyrimidine and O-2-diethylamino-6-methylpyrimidin-4-yl o-methyl-phosphorothioate (U.S. EPA, 2001). In soil, the major metabolite is the parent hydroxypyrimidine (IV) together with smaller amounts of the related compounds (V) and (VI). Compound (IV) is the major degradation product in water with only trace quantities of the P=0 analogue (III) detected (WHO/FAO, 1974).

In humans, pirimiphos-methyl is broken down into the degradation products desethyl pirimiphos-methyl and pirimiphos-methyloxon, which are also active and have transient stability (WHO/FAO, 1983). When pirimiphos-methyl is broken down in rats and dogs, the major urinary metabolite (30 percent of administered dose) was 2-ethylamino-4-hydroxy-6-methylpyrimidine. Other metabolites included 4-0(2-diethylamino-6-methylpyrimidinyl-ß-D-glucosiduronic acid (11 percent of dose in dogs), an unidentified phosphorus-containing product likely to be a dealkylated derivative of either pirimiphos-methyl or its oxygen analogue (12 percent of dose in rats), and 2-amino-4-hydroxy-6-methyl pyrimidine (8 percent of dose in rats and 5 percent of dose in dogs) (WHO/FAO, 1992).

SHELF LIFE

Under normal storage conditions at room temperature, pirimiphos-methyl is stable for up to 6 months. However, it decomposes in sunlight (WHO/FAO, 1983).

ENVIRONMENTAL BEHAVIOR

FATE AND TRANSPORT IN TERRESTRIAL SYSTEMS

Pirimiphos-methyl has limited mobility and persistence in soil (WHO/FAO, 1974). For a variety of soil types, pirimiphos-methyl has a half-life of less than one month (WHO/FAO, 1974). It hydrolyzes rapidly in acidic soils and is stable in neutral and alkaline environments with a half-life of 7.3 days at pH 5, 79 days at pH 7, and 54–62 days at pH 9 (U.S. EPA, 2001). Pirimiphos-methyl decomposes in sunlight (WHO/FAO, 1983).

FATE AND TRANSPORT IN AQUATIC SYSTEMS

Pirimiphos-methyl is not expected to have a significant impact on water resources due to the lack of significant outdoor uses (U.S. EPA, 2001). It degrades in water mainly by hydrolysis, which is attenuated by sunlight. In sunlight, 50 percent degradation occurs within one day. Volatilization also occurs from still water; however, it is not as significant as hydrolysis (WHO/FAO, 1974).

HUMAN HEALTH EFFECTS

ACUTE EXPOSURE

Effects/Symptoms

Similar to other organophosphates, pirimiphos-methyl is a cholinesterase inhibitor and interferes with the normal functioning of the nervous system. It causes dose-related reversible decreases in plasma, red blood cell, and brain cholinesterase at very low doses by ingestion, dermal, and inhalation exposures. It is of

relatively low acute oral, dermal, and inhalation toxicity (U.S. EPA, 1999b). In two human studies, volunteers were fed a dose of 0.25 mg/kg/day for up to 56 days. Marginal plasma cholinesterase depression was observed after both dosing periods (U.S. EPA, 1998b, 2006). However, these studies have many deficiencies and should be used as supplemental data. When compared to animal data, they provide some evidence that humans may be more sensitive than animals as is indicated by the lower effect level for cholinesterase inhibition in humans (U.S. EPA, 1999b). No human poisonings from mishaps with pirimiphos-methyl have been reported (WHO/FAO, 1983).

Animal studies have shown that pirimiphos-methyl is only slightly toxic following acute oral and dermal exposures, with reported LD_{50} values in rats of >2,400 mg/kg (U.S. EPA, 1999a). Other reported oral LD_{50}s are as follows: rabbit (male) 1,154–2,300 mg/kg, mouse (male) 1,020–1,360 mg/kg, guinea pig (female) 1,000–2,000 mg/kg, dog (male) > 1,500 mg/kg, and cat (female) 575–1,150 mg/kg. The reported dermal LD_{50} is > 4,500 mg/kg in female rats (WHO/FAO, 1983), >4,050 mg/kg in female rabbits, and 2,200–4,050 mg/kg in male rabbits (U.S. EPA, 2001, 1999a, 1998a). The reported acute inhalation LC_{50} is > 4.7 mg/L for rats (U.S. EPA, 2001, 1999a, 1998a). Among mammals, no one species appears to be more susceptible. However, the hen is appears to be highly susceptible with a reported LD_{50} of 79–80 mg/kg (WHO/FAO, 1983). Clinical signs of exposure include neurotoxicity, excessive salivation, abnormal gait, ataxia, and leg paralysis. Dermal exposure also decreased plasma cholinesterase levels (WHO/FAO, 1983). Eye and skin irritation have been observed in rabbits (U.S. EPA 1999d, 1998b); however, pirimiphos-methyl has not been shown to be a dermal sensitizer in guinea pigs or rats (U.S. EPA, 1998b; WHO/FAO, 1983).

Treatment

Exposure to pirimiphos-methyl may be determined through laboratory tests of urine and blood that measure breakdown products of pirimiphos-methyl in urine or cholinesterase levels in blood. Blood levels of cholinesterase, especially in plasma, are the most useful in diagnosis of poisoning. However, neither urinary or blood tests are specific for pirimiphos-methyl exposure. Early symptoms of pirimiphos-methyl exposure include excessive sweating, headache, weakness, giddiness, nausea, vomiting, stomach pains, blurred vision, slurred speech, and muscle twitching. Symptoms of more severe poisoning may advance to convulsions, coma, loss of reflexes, and loss of sphincter control. Following dermal exposures, the person should stop working and any contaminated clothing should be removed. Exposed areas of skin should be washed with soap and water and flushed with large quantities of water. For oral exposures, vomiting should not be induced unless a potential lethal dose has been ingested and the person is conscious. Care should be taken as the vomitus may contain toxic amounts of the chemical. Once under medical care, potential lethal doses should be treated by rapid gastric lavage unless the patient is already vomiting. Any ocular exposure should be treated by washing with isotonic saline. If no respiratory insufficiency is noted, peripheral symptoms should be treated with 2–4 mg of atropine sulfate and 1,000–2,000 mg pralidoxime chloride or 250 mg toxogonin (adult dose) by slow intravenous injection. If severe respiratory difficulties, convulsions, and unconsciousness are present, atropine and a reactivator should be given immediately. The airway should be maintained. Morphine, barbiturates, phenothiazine, tranquillizers, and central nervous system stimulants are all contraindicated (WHO/FAO, 1983).

CHRONIC EXPOSURE

NONCANCER ENDPOINTS

Workers in two WHO-supervised health spray program did not show any signs of pesticide poisoning; however, at the end of one of the programs, plasma cholinesterase activity was 70–75 percent of the mean of pre-exposure values. The people living in the spray areas exhibited no signs of poisoning and no effect on cholinesterase activity. Volunteers exposed to 0.25 mg/kg/day for up to 56 days exhibited no toxic effects on

liver function or blood tests and an acceptable daily intake (ADI) of 0.01 mg/kg was established (WHO/FAO, 1983).

Chronic exposure data in animals indicates that a main target of pirimiphos-methyl toxicity is the nervous system. Rats repeatedly exposed to high doses of pirimiphos-methyl showed a cumulative inhibitory effect on cholinesterase (WHO/FAO, 1983). In 90-day and 2-year dietary studies in rats, plasma cholinesterase and some erythrocyte and brain cholinesterase inhibition was reported. In a 2-year dog study and an 80-week mouse study, similar effects were observed (WHO/FAO, 1983).

In developmental and reproductive toxicity studies in rats and rabbits, maternal/parental NOELs were less than or the same as offspring NOELs. No increased sensitivity was noted in fetuses or pups. There is no evidence that pirimiphos-methyl is teratogenic in rat or rabbit feeding studies (U.S. EPA, 1998b, 2006; WHO/FAO, 1983). In several mammalian studies, no mutagenic potential was observed (U.S. EPA, 1998b; WHO/FAO, 1983).

CANCER ENDPOINTS

EPA determined that the carcinogenic potential of pirimiphos-methyl could not be determined because a reliable rat carcinogenicity study is lacking (U.S. EPA, 1998b). In an 80-week mouse feeding study, a 78-week mouse feeding study, a 80-week mouse oral study, a 2-year rat feeding study, a 78-week rat feeding study, and a 2-year oral dog study, no evidence of carcinogenic potential was identified (WHO/FAO, 1983; U.S. EPA, 1998b, 2006). Additionally, mammalian mutagenicity studies do not provide any evidence that supports a carcinogenic potential for pirimiphos-methyl (WHO/FAO, 1983).

TOXICOKINETICS

Pirimiphos-methyl can be absorbed via the gastrointestinal tract, the skin, or, less commonly, by inhalation of fogs, smokes, or spray mists. It is rapidly metabolized and excreted. Pirimiphos-methyl is broken down into desethyl pirimiphos-methyl and pirimiphos-methyloxon, which are also active and have transient stability. In rats dosed with radiolabeled pirimiphos-methyl, 70 percent was excreted within 24 hours and 100 percent was excreted within 5–6 days. Excretion was mainly in the urine (85 percent) and to a lesser extent, feces (15 percent). Pirimiphos methyl and its metabolites do not accumulate in the liver, kidneys, or fatty tissues of rats and domestic animals following oral exposure (WHO/FAO, 1983).

ECOLOGICAL EFFECTS

ACUTE EXPOSURE

Pirimiphos-methyl is not expected to pose a hazard to birds and mammals from acute exposure, because of lack of exposure. In the laboratory, pirimiphos-methyl exhibits relatively high toxicity to birds (WHO/FAO, 1983). Acute oral LD_{50} values in various bird species include chickens (79–80 mg/kg), Japanese quail (140 mg/kg), and green finches (200–400 mg/kg). Dietary LD_{50}s of 630 mg/kg for mallard ducks and 206 mg/kg for bobwhite quail chicks were identified. No lasting adverse effect on hens; chicks; or egg production, quality, or hatchability was seen in studies of chickens fed 4–40 ppm in their diet (WHO/FAO, 1983).

When used for its registered purposes, pirimiphos-methyl is not expected to result in significant exposures of aquatic organisms (U.S. EPA, 2001). Additionally, any risk would be mitigated by its strong tendency to decompose in water and to undergo photo-oxidation (WHO/FAO, 1983). In static tests, the reported 48-hour LC_{50} was 1.4 mg/L in carp and 0.25 mg/L in rainbow trout. The 24-hour LC_{50} for carp was 1.6 mg/L. In flow-through tests, the reported 48-hour LC_{50} was 4.1 mg/L in fathead minnow and 0.53 mg/L in rainbow trout, while the 24-hour LC_{50} was 5.6 mg/L in fathead minnow and 0.78 mg/L in rainbow trout (WHO/FAO, 1983).

CHRONIC EXPOSURE

Due to low risk of both terrestrial and aquatic acute ecological effects of pirimiphos-methyl, serious adverse effects are not anticipated from chronic exposures. Subchronic 90-day exposure of birds to oral doses of up to 10 mg/kg did not result in clinical or histopathological findings (WHO/FAO, 1983).

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PROFILE FOR PROPOXUR:

CAS REGISTRY NUMBER 114-26-1

SUMMARY OF INSECTICIDE

CHEMICAL HISTORY

Propoxur is a broad spectrum, nonsystemic carbamate insecticide that was first introduced in 1959. It is used by homeowners and pest control operators in both agricultural and nonagricultural applications to kill a variety of chewing and sucking pests, mosquitoes, ants, flies, cockroaches, hornets, crickets, and lawn and turf insects (U.S. EPA, 1997a, 2000; EXTOXNET, 1996). Propoxur (Baygon) was first registered in the United States for pesticide use in 1963 and currently there are two registered technical products, several manufacturing use only products, and 173 registered products containing propoxur (U.S. EPA, 1997b).

Propoxur exhibits its toxic effects through reversible cholinesterase inhibition (U.S. EPA, 2000). It has moderate toxicity in mammals (WHO/FAO, 1976), high toxicity in birds, and moderate toxicity in fish (EXTOXNET, 1996; U.S. EPA, 1997b). Short-term exposures may cause effects on the nervous system, liver, and kidneys (IPCS, 1994). In humans, symptoms of acute oral poisoning include red blood cell cholinesterase inhibition with mild transient cholinergic symptoms including nausea, vomiting, sweating, blurred vision, and tachycardia. Long-term inhalation exposures in humans results in cholinesterase inhibition, headaches, nausea, and vomiting (U.S. EPA, 2000). Propoxur pesticides are available as emulsifiable concentrates, wettable powders, dusts and powders, baits, aerosols, fumigants, granular baits, containerized baits, pest strips, shelf paper, pet flea collars, and oil sprays (EXTOXNET, 1996; U.S. EPA, 1997a). Applications methods include aerosol can and injection tube; concentrated liquid using a compressed air sprayer or hand or power sprayer; wettable powder using a ready-to-use sprayer liquid, a power or had pressurized sprayer, or a low pressure sprayer for oil soluble liquid (U.S. EPA, 1997b).

DESCRIPTION OF DATA QUALITY AND QUANTITY

Extensive review data for propoxur are limited. Relevant resources include

- Propoxur: Registration Eligibility Decision (RED) Document (U.S. EPA, 1997b)
- IRIS summary review (U.S. EPA, 2006)
- Pesticide Information Profile for Propoxur (EXTOXNET, 1996)
- Data Sheet on Pesticides. No. 25: Propoxur (WHO/FAO, 1976)
- International Safety Cards: Propoxur (IPCS, 1994).

EPA has developed quantitative human health benchmarks (acute and chronic oral RfDs and short-, intermediate-, and long-term dermal and inhalation benchmarks) for propoxur.

SUMMARY TABLE

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute, Intermediate, Chronic	Inhalation	0.004	mg/kg/day	Inhalation NOEL (2.2 mg/m^3) for neurological effects in rats, adjusted for intermittent	U.S. EPA (1997b)

				exposure and UF of 100 applied	
Acute, Intermediate, Chronic	Oral	0.005	mg/kg/day	Chronic RfD based on LOEL in humans with UF of 30 applied	U.S. EPA (1997b)
Acute, Intermediate, Chronic	Dermal	10	mg/kg/day	Dermal NOAEL for toxicity in rabbits with UF of 100 applied	U.S. EPA (1997b)
Cancer	Inhalation, Oral, Dermal	0.0037	per mg/kg/day	Cancer slope factor based on male rat bladder tumors	U.S. EPA (1997b)

For inhalation exposure, a NOEL of 2.2 mg/m^3 (2.4 mg/kg/day)[7] was identified in rats exposed to propoxur (Pauluhn, 1992, 1994) via inhalation for 6.3 hours per day, 5 days per week for 2 years. Significant plasma, red blood cell, and brain cholinesterase inhibition were observed at higher concentrations (U.S. EPA, 1997b). The concentration was adjusted for intermittent exposure[8] (0.4 mg/kg/day) and an uncertainty factor of 100 was applied to account for interspecies and intrahuman variation, for an inhalation benchmark of 0.004 mg/kg/day. This value is appropriate for all exposure durations. However, the vapor pressure of propoxur is extremely low and significant human exposure via inhalation is not expected (U.S. EPA, 1997b).

For oral exposure, the chronic oral RfD of 0.005 mg/kg/day was calculated based on a LOEL of 0.15 mg/kg for a 40 percent red blood cell cholinesterase inhibition reported in a human exposure study (Vandekar et al., 1971) with an uncertainty factor of 30 applied to account for intrahuman variability (10) and the use of a LOEL (3) (U.S. EPA, 1997b). This value is appropriate for all exposure durations.

For dermal exposure, a NOEL of 1,000 mg/kg/day for lack of toxic effects in a subchronic rabbit study (Diesing and Flucke, 1989) is appropriate for all exposure durations (U.S. EPA, 1997b); an uncertainty factor of 100 was applied to account for interspecies and intrahuman variability. This value is appropriate for all exposure durations. However, studies indicate a very low absorption potential (<20 percent in humans) and/or hazard by the dermal exposure route (U.S. EPA, 1997b).

EPA classified propoxur as a Group B2 chemical, probable human carcinogen. EPA calculated a unit risk of 3.7 x 10^{-3} per mg/kg/day based on bladder tumors in male rats (U.S. EPA, 1997b).

INSECTICIDE BACKGROUND

CAS #: 114-26-1

Synonyms: o-isopropoxyphenyl methylcarbamate (IUPAC); 2-(1-methylethoxy) phenyl methylcarbamate (CA) (WHO, 2005; U.S. EPA 1997b) 2-Isopropoxyphenyl methylcarbamate Phenol, 2-(1-methylethoxy)-,methylcarbamate, Phenol, o-isopropoxy-, methylcarbamate, Propoxur [Phenol, 2-(1-

[7] Conversion between mg/m^3 and mg/kg/day assumes, for Wistar rats, an average body weight of 0.187 kg and inhalation rate of 0.2 m^3/day (U.S. EPA, 1988).

[8] Adjustment for intermittent exposure is the product of air concentration and exposure of 6.3/24 hours/day and 5/7 days/week.

	methylethoxy) -, methylcarbamate 2-(1-Methylethoxy)phenyl methylcarbamate PHC (PAN, 2005; IPCS, 1994)
Chemical Group:	carbamate (EXTOXNET, 1996; U.S. EPA 1997b)
Registered Trade Names:	Trade and other names for propoxur include: Arprocarb, Bay, Bay 9010, Bay 5122, Bay 9010, Baygon, Bayer 39007, Bifex, Blattanex, Blattosep, Brifur, Bolfo, BO Q 5812315, Chemagro 9010, Compound 39007 , Dalf dust , DMS 33, ENT 25671, Invisi-Gard, OMS 33, PHC (JMAF), Pillargon, Prentox Carbamate, Propogon, Proprotox, Propyon, Rhoden, Sendra, Sendran, Suncide, Tendex, Tugon, Fliegenkugel, UN Carbamate, Unden, and Undene (WHO, 2005; PAN, 2005; EXTOXNET, 1996; IPCS, 1994; WHO/FAO, 1976; IPCS, 1973)

USAGE

Propoxur is a residual carbamate insecticide that has a variety of indoor uses, including the control of mosquitoes, ants, cockroaches, crickets, flies, bees, hornets, wasps, ticks, yellow jackets, bedbugs, fleas, woodlice, and spiders (U.S. EPA, 1997b; WHO, 2005; WHO/FAO, 1976). Indoor food applications include only crack and crevice treatment in food areas (U.S. EPA, 1997b). There are limited outdoor applications consisting mostly of perimeter and spot treatments of nests and lawn and turf insects (U.S. EPA, 1997b, 2000). Crop applications include sugar cane, cocoa, grapes, other fruit, maize, rice vegetables, cotton, lucerne, forestry, and ornamentals (WHO, 2005). Propoxur is used in the control of malaria and in pet flea collars (U.S. EPA, 2000). In public health and agricultural applications, propoxur is applied as a dust or by spraying (WHO, 2005). It is available in commercial products as a single active ingredient or combined with other pesticides (U.S. EPA, 1997b).

FORMULATIONS AND CONCENTRATIONS

Common formulations of pesticides containing propoxur include technical grade propoxur, emulsifiable concentrates, wettable powders, baits, aerosols, fumigants, granules, and oil sprays (EXTOXNET, 1996). Typical formulations and percent propoxur content include ready-to-use liquid (0.5–1 percent), pressurized aerosol liquid (0.25–2 percent), oil-soluble liquid/liquid concentrate (8–19.6 percent propoxur), pastes (2 percent), wettable powders (70 percent), solid baits (0.25–2 percent), pet flea collars (impregnated plastic) (0.4–10 percent), impregnated shelf papers (1 percent), and insecticidal tapes (10 percent) (U.S. EPA, 1997b). Common formulations used for agricultural, horticultural, and forestry applications include wettable powders (50 percent), dusts (1–2 percent), granules, oils, emulsifiable concentrates (200 g/L; 20 percent w/w), pressurized sprays, smokes, baits (various concentrations) (WHO/FAO, 1976; IPCS, 1973).

WHO (2005) indicated that the propoxur content in various preparations should be declared and contain the following:

- Technical grade propoxur: not less than 980 g/kg
- Wettable Powder: 500 g/kg $\pm$ 5% of the declared content.

SHELF LIFE

Propoxur is reported to be stable under normal storage and use conditions (IPCS, 1973) but unstable in highly alkaline media. The half-life propoxur is reported as 40 minutes at pH 10 at 20^{o}C (WHO/FAO, 1976).

WHO (2005) reported that following storage at 54 ± 2°C for 14 days, 97 percent or greater of the active ingredient must be present in wettable powder formulations.

DEGRADATION PRODUCTS

In vivo, propoxur is biotransformed by depropylation to 2-hydroxyphenol-N-methylcarbamate and by hydrolysis to the phenol. The glucuronides detected in urine are accounted for by ring hydroxylation and isopropoxy hydroxylation followed by conjugation. Major metabolites in rats include 5-hydroxy-2-isopropoxyphenyl n-methylcarbamate, 2-hydroxyphenyl n-methylcarbamate, o-isopropoxyphenol, o-isopropoxyphenyl, and n-hydroxymethylcarbamate. In mice, the major metabolies include o-isopropoxyphenyl n-hydroxymethylcarbamate. In bean plants, the major metabolites include 4-hydroxy-2-isopropoxyphenyl n-methylcarbamate, 2-hydroxytphenyl n-methylcarbamate, and o-isopropoxyphenyl n-hydroxymethlycarbamate (HSDB, 2005). Limited human data are available. Many propoxur metabolites were found in the urine of a person attempting suicide by ingestion of a large quantity of the emulsifiable concentrate formulation. These were present both as free compound or conjugated with glucuronide or sulfate. As in other species, biotransformation was from depropoxylation, hydrolysis of the ester bond and ring hydroxylation (IPCS, 1989).

ENVIRONMENTAL BEHAVIOR

FATE AND TRANSPORT IN TERRESTRIAL SYSTEMS

Propoxur is expected to be moderately to very highly mobile and moderately persistent in soil (HSDB, 2005; U.S. EPA, 1997a, 1997b; EXTOXNET, 1996). With a K_{oc} ranging from <1 to 103, high to very high mobility is expected if propoxur is released in soil (HSDB, 2005); however, the mobility depends on the soil type and previous exposures to propoxur. Biodegradation in soil is more rapid in previously exposed soils. In many soil types, propoxur is highly mobile due to its low affinity for soil binding (EXTOXNET, 1996; U.S. EPA, 1997a, 1997b). It evaporates from soil, with the amount increasing with the moisture content of the soil, and the half-life is 6–8 weeks, depending on the soil type (IPCS, 1973). Data from studies of the persistence of propoxur in several soil types suggest that it moves rapidly through all soil profiles below the 12 inch sampling depth. Its fate and transport characteristics are similar to those chemicals that are known to leach into groundwater (U.S. EPA, 1997b).

Hydrolysis appears to be the primary mode of degradation (U.S. EPA, 1997b). At neutral pH, propoxur is hydrolically stable but degrades rapidly at alkaline pH values (U.S. EPA, 1997b). Half-life values of a propoxur in aqueous solutions at 20°C are reported to range from 1 minute at pH 12.8 to 40 minutes at pH 10.8 (IPCS, 1973). Half-life values of 16 days at pH 8, 1.6 days at pH 9, and 0.17 days at pH 10 are reported (U.S. EPA, 1997b). Volatilization is not expected to be a major fate process from moist soil surfaces (HSDB, 2005). The major fate process in moist soils is biodegradation. Under aerobic conditions, biodegradation half-lives of 80 days in silt loam soil and 120 days in sandy loam soil are reported (HSDB, 2005). On inert surfaces, however, volatilization is the main fate process. On a glass surface, 50 percent of a propoxur residue was still present 1.8 hours after application (IPCS, 1973). Propoxur in soil shows no or little susceptibility to photolysis (U.S. EPA, 1997b; IPCS, 1973). Half-lives of several months were reported for the degradation of propoxur under aerobic and anaerobic conditions (U.S. EPA, 1997b).

FATE AND TRANSPORT IN AQUATIC SYSTEMS

Propoxur is highly soluble in water and there is a high likelihood of groundwater penetration because it does not adsorb strongly to soil particles (HSDB, 2005; EXTOXNET, 1996; U.S. EPA, 1997a). It is relatively stable in water at pH 7 or less but hydrolyzes rapidly at pHs greater than 7 (IPCS, 1973). In a 1 percent aqueous solution at pH 7, propoxur hydrolyzes at a rate of 1.5 percent per day (EXTOXNET, 1996).

Reported field half-lives for propoxur are 14–50 days (EXTOXNET, 1996). The hydrolysis half-life of propoxur is reported to be 1 year at pH 4, 93 days at pH 7, and 30 hours at pH 9 (HSDB, 2005). Volatilization from water is not expected to be a major fate process. However, propoxur is susceptible to photolysis in water (U.S. EPA, 1997b). The half-life of propoxur irradiated with light more than 290 nm is reported as 88 hours (HSDB, 2005). Because propoxur degrades rapidly in water, bioconcentration in fish is unlikely (HSDB, 2005).

HUMAN HEALTH EFFECTS

ACUTE EXPOSURE

Effects/Symptoms

Propoxur causes its toxic effects by reversible inhibition of cholinesterase. Short-term exposures may cause effects on the nervous system, liver, and kidneys (IPCS, 1994). In humans, symptoms of acute oral poisoning include red blood cell cholinesterase inhibition with mild transient cholinergic symptoms including nausea, vomiting, sweating, blurred vision, and tachycardia (U.S. EPA, 2000). Limited data exist on the human health effects of acute exposure to propoxur. In volunteers, a single oral dose was reported to cause stomach discomfort, sweating, and redness of the face. However transient erythrocyte cholinesterase activity inhibition (up to 27 percent) was observed at a higher level and was associated with vomiting, sweating, and blurred vision (WHO/FAO, 1976). When used to control for malaria, spray operators experienced occasional short-lasting symptoms including nausea, headache, sweating, and weakness from which they quickly recovered (WHO/FAO, 1976; EXTOXNET, 1996). Additionally, some mild reactions were reported by residents where it was applied (WHO/FAO, 1976).

In animals, propoxur is acutely toxic via the oral, inhalation, and dermal routes (U.S. EPA 1997b, 2000; EXTOXNET 1996). Acute inhalation and dermal exposures are moderate to highly toxic while oral exposures are highly to be extremely toxic (U.S. EPA, 1997a, 2000). Propoxur is highly toxic to animals via ingestion. In rats, the oral LD_{50} for propoxur ranges from 68 mg/kg in females to 116 mg/kg in males (EXTOXNET, 1996; WHO/FAO, 1976; U.S. EPA, 1997b). In other species, reported oral LD_{50} values include approximately 100 mg/kg in mice and 40 mg/kg in guinea pigs (EXTOXNET, 1996). Reported dietary levels causing no toxic effects in animals include 300mg/kg/day for mice, 10 mg/kg/day for rats, and 5 mg/kg/day for dogs (IPCS, 1989). Via the dermal route, the reported LD_{50} values in various species include greater than 2,400 mg/kg in rats (EXTOXNET, 1996; WHO/FAO, 1976) and 500 mg/kg to > 2000 mg/kg in rabbits (EXTOXNET, 1996; U.S. EPA, 1997b). Via inhalation, the reported LC_{50} values include a 4-hour LC_{50} of >0.5 mg/L in rats (U.S. EPA, 1997b) and a 1-hour LC_{50} of > 1.44 mg/L (EXTOXNET, 1996).

Similar to its effects in humans, acute exposure to propoxur in animals causes symptoms typical of cholinesterase inhibition (EXTOXNET, 1996; U.S. EPA, 1997b). Cholinesterase depression, muscle spasms, and salivation have been reported within 10 minutes of oral administration in rats (U.S. EPA, 1997b). In rats fed propoxur in their diet for 16 weeks, whole blood cholinesterase was inhibited at dietary levels over 500 ppm while plasma, whole blood, and brain cholinesterase were inhibited at dietary levels greater than 1,000 ppm at study termination. Signs of cholinesterase inhibition were also observed in both rats and mice within 15 minutes of exposure to different concentrations of propoxur aerosol (WHO/FAO, 1976). Brain pattern and learning ability changes can occur at lower concentrations than those that cause cholinesterase inhibition and/or organ weight changes (EXTOXNET, 1996).

Although propoxur is a mild eye irritant in rabbits, it is not a skin irritant in rabbits or a dermal sensitizer in guinea pigs (U.S. EPA, 1997b). Acute exposure to propoxur is not considered to be teratogenic in rats (WHO/FAO, 1976).

TREATMENT

Exposure to propoxur may be determined through laboratory tests that determine cholinesterase levels in blood with erythrocyte cholinesterase being a more informative indicator than either plasma or whole blood. However, the enzyme will only be inhibited for a few hours following exposure. Additionally, phenol metabolites may be determined in urine (WHO/FAO, 1976; U.S. EPA, 2000). However, neither of these tests are reliable indicators of total exposure because they are not specific for propoxur (U.S. EPA, 2000).

Propoxur poisoning should be treated by first removing any contaminated clothing, and washing affected skin with soap and water and flushing the area with large amounts of water (WHO/FAO, 1976; IPCS, 1994). If propoxur gets in the eyes, they should be rinsed immediately with isotonic saline or water. Contact lenses should be removed, if possible. Oral exposure to propoxur should be treated by administration of activated charcoal (HSDB, 2005; IPCS, 1994). Rapid gastric lavage with 5 percent sodium bicarbonate is indicated if the patient is not already vomiting. Medical attention should be sought (WHO/FAO, 1976; HSDB, 2005). Inhalation exposures should be treated by removal to fresh air, placing in a half-upright position, monitoring for respiratory distress, and seeking medical attention (HSDB, 2005; IPCS, 1994). Because propoxur is quickly metabolized and symptoms are of a short duration, atropine treatment is not usually necessary by the time the patient reaches medical help (WHO/FAO, 1976). However, adults showing signs of propoxur toxicity should be treated with 1–2 mg atropine sulfate given intramuscularly or intravenously as needed. Oxygen may be necessary for unconscious patients or those in respiratory distress. Pralidoxime is usually not necessary unless the poisoning is severe. Barbiturate and central stimulants are contraindicated (HSDB, 2005; WHO/FAO, 1976).

CHRONIC EXPOSURE

NONCANCER ENDPOINTS

Limited data are available on the effects of chronic exposure to propoxur in humans. Chronic effects are expected to be similar to acute effects (EXTOXNET, 1996). Cholinesterase inhibition, headaches, vomiting, and nausea were reported in humans following chronic inhalation exposure (U.S. EPA, 2000). When used to control for malaria, spray operators experienced occasional short lasting symptoms including nausea, headache, seating, and weakness from which they quickly recovered (WHO/FAO, 1976). No data are available on human reproductive or developmental effects (U.S. EPA, 2000).

In animals, propoxur is quickly detoxified and does not accumulate in body tissues over time. Daily doses approximating the LD_{50} have been tolerated by rats for long periods of time when the dose was given over the course of the day (EXTOXNET, 1996; WHO/FAO, 1976). Chronic oral exposure to propoxur in animals has been reported to cause cholinesterase inhibition, decreased body weight, liver and bladder effects, and a small increase in neuropathy (U.S. EPA, 1997b, 2000; WHO/FAO, 1976). Significant plasma, red blood cell, and brain cholinesterase inhibition was observed in male and female rats exposed to propoxur in air over a 2-year period (U.S. EPA, 1997b).

The nervous system and liver are the main organs affected by propoxur in both humans and animals (EXTOXNET, 1996). Increased liver weights were observed in rats fed propoxur in feed for 2 years (WHO/FAO, 1976). Reproductive and developmental effects have not been reported in rabbits orally exposed to propoxur. However, some fetotoxicity, decreased litter size, central nervous system impairment in offspring, and decreased fetal weights have been reported in rats orally exposed to propoxur (U.S. EPA, 1997b, 2000; WHO/FAO 1976). The data indicate that reproductive effects in humans are not expected at typical exposure levels and teratogenic effects will occur only at high levels (EXTOXNET, 1996). The available data indicate that propoxur is not mutagenic (EXTOXNET, 1996; U.S. EPA, 1997a).

CANCER ENDPOINTS

EPA's OPP has classified propoxur as Group B2, probable human carcinogen, with a unit risk of 3.7 x 10^{-3} per mg/kg/day (U.S. EPA, 1997a, 1997b). No information is available on the carcinogenicity of propoxur in humans (U.S. EPA, 2000). A significant increase in bladder papillomas and/or carcinomas was reported in male rats while a significant increase in hepatocellular adenomas and combined adenoma/carcinoma was reported in male mice (U.S. EPA, 1997b, 2000). High dose exposure to propoxur is also associated with an increase in tumors of the uterus (U.S. EPA, 2000).

TOXICOKINETICS

Like most carbamates, propoxur can be absorbed through the oral, inhalation, and dermal pathways (HSDB, 2005; IPCS, 1994; WHO/FAO, 1976). It is readily absorbed by the lungs (HSDB, 2005) and gastrointestinal tract (IPCS, 1994) but to a lesser extent through the skin (WHO/FAO, 1976). Dermal rat studies indicate that absorption decreases with dose in a nonlinear way. Absorption of a dermal dose of 6.91 μg/cm² was 7.88, 10.2, 17.9, 23.2 and 32.5 percent for durations of 0.5, 1, 2, 4, 8, and 32 hours, respectively, which was a higher rate of absorption than in human studies of 8 and 24 hour exposures. Human studies indicate that the rate of 19.6 percent absorption most closely approximates the rate expected in the field (U.S. EPA, 1997b). Approximately 16 percent of the dose of radiolabeled propoxur applied to the forearms of volunteers was available for percutaneous absorption (HSDB, 2005). Additionally, the rate of dermal absorption is affected by the solvent used (U.S. EPA, 1997b).

Propoxur and its metabolites are distributed by the lymph system. Metabolism studies in rats exposed to radiolabeled propoxur have shown radioactivity in all organs (especially the intestines) except bones at 1 hour. High concentrations of radioactivity were still present in the gastrointestinal tract, bladder, and mucous membranes of the pharyngeal system after 24 hours. Some radioactivity was still present in the liver, kidneys, and mucous membranes of the pharyngeal region at 48 and 72 hours (U.S. EPA, 1997b). Peak concentrations were seen in the blood (at 15 minutes), brain (1 hour), liver (4 hours), and kidneys (6 hours) after oral exposure to 50 mg/kg propoxur, with the highest concentrations seen in the kidneys and the lowest concentration in the brain (HSDB, 2005). Ingested propoxur is rapidly absorbed, broken down, and excreted in the urine (EXTOXNET, 1996; U.S. EPA 1997b). The major routes of metabolism in rats are depropylation to 2-hydroxyphenyl-N-Methylcarbamate and hydrolysis to isopropoxyl phenyl. Peak circulating and tissue concentrations of isopropxyl phenol were achieved 30–60 minutes after a single oral dose in rats (HSDB, 2005). Because of its rapid metabolism and excretion, propoxur does not accumulate in mammalian tissues (EXTOXNET, 1996). The main route of excretion for propoxur is probably the urine (WHO/FAO, 1976) accounting for 60–95 percent of the dose (HSDB, 2005). In humans, 38 percent of a single oral dose of Baygon was excreted in the urine within the first 24 hours. Of that, most was excreted by the first 8–10 hours (EXTOXNET, 1996). In dermal studies in humans, total excretion was 19.6 percent of the total dermal dose (U.S. EPA, 1997b). Lesser amounts of propoxur are excreted as carbon dioxide (20–26 percent) and in feces (4 percent) (HSDB, 2005).

ECOLOGICAL EFFECTS

ACUTE EXPOSURE

Acute exposure to technical grade propoxur is very highly toxic to many bird species (EXTOXNET, 1996; U.S. EPA, 1997b). Remarkable variation in the results of dietary studies of the toxicity of propoxur has been reported. Oral LD_{50} values for 97 percent ai in a 2 percent bait product range from 4.2 mg ai/kg body weight in mourning doves to 120 mg ai/kg body weight in sharp-tailed grouse (U.S. EPA, 1997b; EXTOXNET, 1996). An unexplained phenomenon where, in some instances, birds of a given species are able to metabolize

propoxur has been reported. U.S. EPA (1997b) indicated more confidences in the LD_{50} values for Mallard ducks (9.44 mg ai/kg) and Bobwhite quail (1,005 mg ai/kg formulated product). In the diet, subacute 5-day LC_{50} values range from 206 ppm in Northern bobwhite quail exposed to an unknown concentration to greater than 5,000 ppm in Mallard ducks exposed to 98.8 percent ai and Japanese quail exposed to an unknown concentration (U.S. EPA, 1997b). The reported oral LD_{50} in mule deer is 100–350 mg/kg (EXTOXNET, 1996). Additionally, propoxur has been found to be highly toxic to honeybees (EXTOXNET, 1996).

Propoxur is expected to pose a minimal risk to aquatic organisms because of its limited outdoor bait use (U.S. EPA, 1997b). However, when exposures occur, they pose a slight to moderate acute risks to fish and other aquatic species (EXTOXNET, 1996). In freshwater fish, propoxur is moderately toxic with LC_{50} values ranging from >1–10 ppm (U.S. EPA, 1997b). The reported 96-hour LC_{50} values range from 3.7 ppm in rainbow trout exposed to 98.8 percent ai to 25 ppm in fathead minnow exposed to 88 percent ai (U.S. EPA, 1997b; EXTOXNET, 1996). The 96-hour LC_{50} for bluegill sunfish was reported as of 6.6 mg/L (EXTOXNET, 1996).

Propoxur is more toxic in freshwater and estuarine invertebrates. Acute exposure to technical grade propoxur is very highly toxic to freshwater and estuarine invertebrates with EC/LC_{50} values of 0.011 ppm in daphnids, 0.034 ppm in amphipods, 0.18 ppm in stonefly, and 0.041 ppm in pink shrimp (U.S. EPA, 1997b). An oral LD_{50} of 595 mg/kg was reported for propoxur in bullfrogs (EXTOXNET, 1996).

CHRONIC EXPOSURE

Very little data exist for chronic exposure to propoxur in non-target terrestrial organisms. In birds, no reproductive effects were seen in Northern bobwhite quail fed diets containing greater than 320 ppm (98 percent ai) of propoxur for a number of weeks. No effects on brain cholinesterase were seen at concentrations up to 80 ppm. In Mallard ducks, no reproductive or brain cholinesterase effects were seen in birds fed diets containing 80 ppm (98 percent ai) for 23 weeks. However, reduced egg production and embryo survival were noted at 320 ppm (U.S. EPA, 1997b). Little or no data exist for chronic exposure to propoxur in marine/estuarine organisms. However, no significant accumulation of propoxur is expected in aquatic organisms (EXTOXNET, 1996).

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PROFILE FOR TEMEPHOS:

CAS Registry Number 3383-96-8

SUMMARY

CHEMICAL HISTORY

Temephos is a nonsystemic organophosphate insecticide used in the United States since 1965 for public health reasons (U.S. EPA, 1999b, 2000) to control mosquito, midge, and black fly larvae (EXTOXNET, 1996). It is also used occasionally to treat potable water. Temephos has a low toxicity in mammals, moderate toxicity in birds, and high toxicity in some aquatic organism (HSDB, 2005). All food tolerances for temephos have been revoked (U.S. EPA, 2000). Temephos is available in emulsifiable concentrates (up to 50 percent), wettable powder (50 percent), and granular forms (up to 5 percent) (EXTOXNET, 1996). Because temephos is used primarily as a larvicide to treat bodies of water, the potential for incidental dermal or soil/dust exposure during this usage is minimal (HSDB, 2005). Occupationally exposed workers are the only population with potential elevated risk for temephos exposure due to its limited use pattern and lack of residential, dietary, and drinking water exposures (U.S. EPA, 1999b, 2000; ATSDR, 2005). Although human populations could potentially be exposed to very low levels from potable water that has been treated continually with temephos, little concern exits due to its low toxicity and solubility (ATSDR, 2005).

DESCRIPTION OF DATA QUALITY AND QUANTITY

Because temephos is a new larvicide and has a limited use pattern, extensive review data do not exist. Relevant resources include

- Toxicologic Information About Insecticides Used For Eradicating Mosquitoes (West Nile Virus Control): Temephos (ATSDR, 2005)
- Reregistration Eligibility Decision (RED) Document (U.S. EPA, 2000)
- Pesticide Information Profile for Temephos (EXTOXNET, 1996)
- Specifications and Evaluations for Public Health Pesticides for Temephos (WHO, 1999).

EPA has developed quantitative human health benchmarks (intermediate and chronic oral RfDs and short-, intermediate-, and long-term dermal and inhalation benchmarks) for temephos.

SUMMARY TABLE

Duration	Route	Benchmark Value	Units	Endpoint	Reference
Acute, Intermediate, Chronic	Inhalation	0.003	mg/kg/day	Oral NOEL for neurological effects in rats with UF of 100 applied; assume 100% absorption	U.S. EPA (2000)
Acute	Oral	0.2	mg/kg/day	Adopt intermediate RfD for acute duration	
Intermediate	Oral	0.2	mg/kg/day	Intermediate RfD based on NOAEL in rats with UF of 100 applied	U.S. EPA (1997)
Chronic	Oral	0.02	mg/kg/day	Chronic RfD based on NOAEL in rats with UF of 1000 applied	U.S. EPA (1997)
Acute, Intermediate, Chronic	Dermal	0.003	mg/kg/day	Oral NOEL for neurological effects in rats with UF of 100 applied; assume 38% absorption	U.S. EPA (2000)

For inhalation and dermal exposure, a NOEL of 0.3 mg/kg/day was identified for neurological effects (inhibition of red blood cell [RBC] cholinesterase) in rats fed temephos for 90 days and an uncertainty factor of 100 was applied. This value is appropriate for inhalation and dermal exposures and all exposure durations (U.S. EPA, 2000).

For oral exposure, intermediate and chronic oral RfDs of 0.02 and 0.2 mg/kg/day, respectively, were based on a NOAEL of 200 ppm in rats exposed to 200 ppm in the diet, with uncertainty factors of 100 and 1,000, respectively, applied (U.S. EPA, 1997). The intermediate-duration RfD was adopted to represent acute exposures.

INSECTICIDE BACKGROUND

CAS #:	3383-96-8
Synonyms:	Phosphorothioic acid, O,O'-(thiodi-4,1-phenylene) bis (O,O'-dimethyl) phosphorothioate; Phosphoric acid, O,O'-(thiodi,1,4-phenylene) O,O,O',O'-tetramethyl ester (U.S. EPA, 2000)
Chemical Group:	organophosphate (EXTOXNET, 1996)
Registered Trade Names:	Compounds containing temephos: Abat, Abate, Abathion, Acibate, Biothion, Bithion, Difennthos, Ecopro, Nimitox, and Swebate (EXTOXNET, 1996)

USAGE

Temephos is an organophosphate insecticide that is used to control mosquito larvae. It is used in standing water, shallow ponds, swamps, marshes, intertidal zones, tire piles, and highly polluted waters. There are no registered residential uses for temephos (U.S. EPA, 1999b, 2000). Temephos may also be found in mixed

insecticidal formulations such as trichlorfon (EXTOXNET, 1996). U.S. EPA (2000) has reported the use rates for temephos. Granular temephos may be applied at a maximum of 0.5 lbs/ai (active ingredient) per acre. The typical application of temephos in granular form ranges from 0.1–3 lbs/ai/acre. To treat tire piles, the granular application rate is 0.05 lbs/ai/100 ft^2. As an emulsifiable concentrate, temephos may be applied at a maximum of 1.5 fl. oz/acre (0.0469 lbs/ai/acre). The typical application of temephos in the emulsifiable form is 0.5–1.0 fl. oz/acre (0.0156–0.0313 lbs/ai/acre) (U.S. EPA, 1999b, 2000).

FORMULATIONS AND CONCENTRATIONS

Temephos is available in emulsifiable concentrates (up to 50 percent), wettable powder (50 percent), and granular forms (up to 5 percent) (EXTOXNET, 1996; U.S. EPA, 1999b, 2000). It is most commonly applied from airplanes and helicopters. Other application methods include backpack power blowers and right-of-way sprayers, horn blowers, belly grinders, and spoons (U.S. EPA, 1999b, 2000). WHO (1999) indicated that the temephos content in the various preparations should be declared and contain the following:

- Technical grade temephos: no less than 800 g/kg
- Emulsifiable concentrate: 250–500 g/kg +/- 10% of the declared content or above 500 g/kg +/- 25 g/kg
- Emulsifiable concentrate for simulium control: 200 g/kg +/- 10 g/kg
- Sand granules:10 g/kg +/- 25% of the declared content.

SHELF LIFE

Temephos is reported to be stable indefinitely at room temperature (HSDB, 2005); however, no supporting data on its shelf-life could be located.

DEGRADATION PRODUCTS

In water, temephos degrades slowly, forming degradation products from the sulfide group and the phosphate group through oxidation and hydrolysis, respectively. Hydrolysis occurs in basic or highly acidic water, and temephos is stable in water at pH 5-7. Hydrolysis degradation products include 4,4-thiodiphenol. Photolysis of temephos in methanol through sunlight exposures produces sulfone. A similar reaction may also occur in waters exposed to sunlight. Biodegradation does not occur (HSDB, 2005). Temephos breaks down when heated or burned. Toxic fumes such as phosphorous oxides and sulfur oxides are produced during this process. Temephos reacts strongly with acids and bases (IPCS, 2005).

ENVIRONMENTAL BEHAVIOR

FATE AND TRANSPORT IN TERRESTRIAL SYSTEMS

Based on temephos' very low water solubility and its high affinity for soil, the estimated half-life in soil is around 30 days (EXTOXNET, 1996). The affinity of temephos to soil also suggests that temephos is not extremely mobile in the soil (U.S. EPA, 1999b, 2000). Its very low vapor pressure suggests that it will not significantly volatilize from soil or sediments under most conditions. However, the breakdown products of temephos (temephos sulfoxide, temephos sulfone, temephos sulfide, and sulfone phenols) are more likely to migrate to and remain in water since they do not bind as strongly to soil. In field studies of sediments, temephos was shown to absorb rapidly to organic media and degrade rapidly to low or undetectable concentrations (U.S. EPA, 1999b, 2000). The breakdown of temephos in plants is very slow (EXTOXNET, 1996).

FATE AND TRANSPORT IN AQUATIC SYSTEMS

Temephos is applied to aquatic environments where mosquitoes breed. It has a low water solubility and a low persistence in water. Several studies found that temephos rapidly degrades in natural waters (ATSDR, 2005; U.S. EPA, 1999b, 2000; EXTOXNET, 1996). Microorganisms and exposure to sunlight are the main ways that temephos degrades and dissipates in water, however, in their absence, temephos does not dissipate significantly (U.S. EPA, 1999b, 2000; EXTOXNET, 1996). In water, temephos would take a very long time to volatilize, as indicated by its very low Henry's law constant, suggesting that it would instead partition to sediment or soil. Hydrolysis is expected within a few days in highly basic or acidic conditions, but temephos is expected to persist longer at pH 5–7 (ATSDR, 2005). Temephos is not likely to reach ground water that would be used for drinking water due to its relatively short half-life in natural waters and the lack of mobility in soil. Because temephos binds to fatty substances, it can bioconcentrate in fish (U.S. EPA, 2000).

HUMAN HEALTH EFFECTS

ACUTE EXPOSURE

Effects/Symptoms

Temephos causes its toxic effects by the inhibition of cholinesterase. Typical acute toxicity signs are eye irritation, blurred vision, dizziness, nausea, diarrhea, salivation, headaches, loss of muscle coordination, tremors, and difficulty breathing (EXTOXNET, 1996; U.S. EPA, 1999a, 2000; NIOSH, 2004). Compared to other organophosphates, temephos is of low to moderate toxicity (U.S. EPA, 2000). It is moderately toxic through acute dermal and oral exposures and has low toxicity through inhalation exposure (U.S. EPA, 2000). Few studies exist on the human health effects of acute exposure to temephos, presumably due to its low toxicity in humans (ATSDR, 2005). Human volunteers who ingested 256 mg/day for 5 days or 64 mg/day for 4 weeks exhibited no plasma or erythrocyte cholinesterase inhibition (ATSDR, 2005).

In animals, the target organs of acute temephos exposure are the nervous system and liver (EXTOXNET, 1996). Oral LD_{50} values in various animal species include 400–1,300 mg/kg in rats, 400-4,700 mg/kg in mice (EXTOXNET, 1996), and 5,000 mg/kg in cats and dogs (2 percent powder formulation) (EXTOXNET, 1996). In rabbits, a dermal LD_{50} of 1,850 mg/kg in males or 970 mg/kg in females is reported. Similar to its effects in humans, acute high dose exposure to temephos causes neurological effects in animals due to cholinesterase inhibition (U.S. EPA, 1999a, 2000). Effects of cholinesterase inhibition are generally at exposures of 10 mg/kg/day, with liver and other effects seen at higher exposures. However, a few studies have seen cholinesterase effects as low as 1 mg/kg/day (ATSDR, 2005). Although temephos causes slight eye irritation in animals, no skin irritation or dermal sensitization were observed (U.S. EPA, 1999a, 2000). Acute exposures to temephos are not considered to be reproductive or developmentally toxic (U.S. EPA, 1999a, 2000).

Treatment

Exposure to temephos may be determined through laboratory tests to determine cholinesterase levels in blood (WHO/FAO, 1978). Oral exposure to temephos should be treated by rinsing out the mouth and seeking immediate medical attention. For dermal exposures, any contaminated clothing should be removed and the exposed area should be rinsed and then washed with soap and water. Medical attention should be sought. If temephos gets in the eyes, they should be rinsed immediately with copious amounts of water for several minutes. Contact lenses should be removed if possible and medical attention should be sought. Inhalation exposures require removal to fresh air and rest. Artificial respiration should be performed if the person stops breathing, and medical attention should then be sought immediately (IPCS, 2005; NIOSH, 2004).

CHRONIC EXPOSURE

NONCANCER ENDPOINTS

The effects of chronic exposure to temephos in humans have not been well described in the literature, although it is not expected to be toxic at the levels applied to control for mosquitoes. No effects on cholinesterase (plasma or erythrocyte) levels were also seen in residents of a community exposed to < 1 ppm temephos in their water supply for 19 months. Application of 2 percent temephos powder to human subjects and their bedding was deemed safe and effective (ATSDR, 2005).

Chronic-duration exposure studies in animals have shown that temephos can inhibit cholinesterase levels, with symptoms of poisoning occurring at higher levels. A slight decrease in blood and brain cholinesterase activity was seen in dogs chronically exposed to 3–4 mg/kg/day, while severe effects were seen at 14 mg/kg/day. Decreased liver weights were seen in rats fed small doses of temephos for more than 2 years, and rabbits had minor pathological liver changes at 10 mg/kg/day. Temephos is not expected to cause reproductive, teratogenic or mutagenic effects (EXTOXNET, 1996).

CANCER ENDPOINTS

EPA has not classified temephos as a carcinogen (U.S. EPA, 2000). No data exist on the carcinogenic effect of temephos in humans. The existing data suggest that temephos is not carcinogenic. No tumors were reported in rats fed diets containing up to 15 mg/kg/day for 2 years (U.S. EPA, 1999a, 2000).

TOXICOKINETICS

Temephos can be absorbed through the oral, dermal, and inhalation pathways, with dermal exposure being the most likely and typical (EXTOXNET, 1996). However, in rats, only 38 percent of dermally applied temephos was absorbed (U.S. EPA, 2000). Oral studies in rats have shown that peak bloodstream concentration after a single oral dose of temephos was reached between 5 and 8 hours post-administration, with a half-life of 10 hours. In mammals, most temephos leaves the body unchanged in urine and feces, with only some breakdown products detected (sulfate ester and glucoside conjugates of phenolic hydrolysis) (ATSDR, 2005; EXTOXNET, 1996; WHO/FAO, 1978).

ECOLOGICAL EFFECTS

ACUTE EXPOSURE

Temephos is not expected to have a direct effect on terrestrial animals, because it is applied to water so exposures are expected to be low (U.S. EPA, 1999b, 2000). However, it is toxic to nontarget terrestrial organisms such as birds. In birds, temephos may be highly toxic to some species while only moderately toxic to others. The LD_{50}s temephos ranges from 18.9 to 240 mg/kg in California quail and chucker partridge, respectively. However, no significant changes in reproduction were observed in mallard ducks fed diets that contained moderate amounts of temephos (EXTOXNET, 1996). Temephos has been found to be extremely toxic to bees. The direct contact LC_{50} is 1.55 µg/bee (EXTOXNET, 1996).

Temephos is used in shallow water as a larvicide. It has shown a range of toxicity in the aquatic environment depending on its formulation with the emulsifiable concentrate and wettable powders being the most toxic (EXTOXNET, 1996). In fish, temephos has been shown to be slightly to moderately toxic to a variety of species. The most sensitive were the rainbow trout, with an LD_{50} range of 0.16 to 3.49 mg/L. The 96-hour LD_{50} values for the emulsifiable concentrate in various other fish species range from 0.35 mg/L in coho salmon to 6.7 mg/L in Atlantic salmon. The 96-hour LD_{50} values for technical grade temephos in various

fish species range from > 10 mg/L in channel catfish to 21.8 mg/L in bluegill sunfish (U.S. EPA, 1999b, 2000).

Temephos is a hydrophobic chemical, so it is more likely to bind to fatty substances; as a result, temephos has the potential to bioconcentrate (U.S. EPA, 1999b, 2000). Some data indicate that there was some bioaccumulation in fish after 20 days of exposure, but temephos was no longer detected 14 days after exposure ended (U.S. EPA, 1999b, 2000).

In aquatic invertebrates, temephos is highly to very highly toxic. This is not surprising because it is an insecticide used to control aquatic larval stages of mosquitoes and other pests. One laboratory study using a 5 percent granular temephos formulation indicated that the emulsifiable concentrate is much more toxic to marine/estuarine aquatic invertebrates than granular formulations (U.S. EPA, 1999b, 2000). The 96-hour LC_{50} values for some freshwater invertebrates include 0.08 mg/kg for Gamma lacustris and 0.01–0.03 mg/kg for stoneflies. One commercial temephos formulation (Abate4E; 46 percent emulsifiable concentrate) is very toxic to saltwater invertebrates, including pink shrimp and oysters. The LC_{50} values for those species are 0.0005 and 0.019 mg/L, respectively. This formulation is not toxic to bull frogs (EXTOXNET, 1996).

CHRONIC EXPOSURE

Very little data exist for chronic exposure to temephos in nonterrestrial target organisms. Currently, no data exist for potential chronic effects in waterfowl or birds exposed via food. The data that do exist indicate there is little impact (U.S. EPA, 1999b, 2000).

Little data exist for chronic exposure to temephos in marine/estuarine organisms. However, because temephos may be replied repeatedly to water, the chronic exposure of fish is of potential concern. Studies have shown that no chronic effects were seen in fish following 10 applications of a commercial temephos formulation (granular Abate® 2G). Another study showed growth retardation in fish following the application of the liquid Abate® 4E formulation (U.S. EPA, 1999b).

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ANNEX F1: EXPOSURE SCENARIOS

Table F1-1. Indoor Residual Spraying Scenarios

ID	Exposure Scenarios	Type	Exposure Route	Receptor	Exposure	Safety
Worker/Operator Scenarios						
W-IRS-1	Mixing/loading of insecticide for	WP or EC	Dermal	Adult woman	Chronic	Guidelines
W-IRS-2	Mixing/loading of insecticide for	WP or EC	Dermal	Adult woman	Chronic	Lax (No PPE)
W-IRS-3	Spray application	Liquid	Inhalation	Adult woman	Chronic	Guidelines
W-IRS-4	Spray application	Liquid	Inhalation	Adult woman	Chronic	Lax (No PPE)
W-IRS-5	Spray application	Liquid	Dermal	Adult woman	Chronic	Guidelines
W-IRS-6	Spray application	Liquid	Dermal	Adult woman	Chronic	Lax (No PPE)
Resident Scenarios						
R-IRS-1	Contact with sprayed surfaces	Residual	Dermal	Adult woman	Chronic	NA
R-IRS-2	Contact with sprayed surfaces	Residual	Dermal	Child	Chronic	NA
R-IRS-3	Contact with sprayed surfaces	Residual	Dermal	Toddler	Chronic	NA
R-IRS-4	Contact with sprayed surfaces	Residual	Oral (hand-to-mouth)	Toddler	Chronic	NA
R-IRS-5	Contact with sprayed surfaces	Residual	Inhalation	Adult woman	Chronic	NA
R-IRS-6	Contact with sprayed surfaces	Residual	Inhalation	Child	Chronic	NA
R-IRS-7	Contact with sprayed surfaces	Residual	Inhalation	Toddler	Chronic	NA
R-IRS-8	Contact with sprayed surfaces	Residual	Inhalation	Infant	Chronic	NA
R-IRS-9	Contact with sprayed surfaces	Residual	Oral (breast milk)	Infant	Chronic	NA

Table F1-2. Long-lasting Insecticidal Net Scenarios

ID	Exposure Scenarios	Type	Exposure Route	Receptor	Exposure	Safety
Resident Scenarios						
R-LLIN-1	Sleeping under a treated net	Residual	Inhalation	Adult woman	Chronic	NA
R-LLIN-2	Sleeping under a treated net	Residual	Inhalation	Child	Chronic	NA
R-LLIN-3	Sleeping under a treated net	Residual	Inhalation	Toddler	Chronic	NA
R-LLIN-4	Sleeping under a treated net	Residual	Inhalation	Infant	Chronic	NA
R-LLIN-5	Sleeping under a treated net	Residual	Dermal	Adult woman	Chronic	NA
R-LLIN-6	Sleeping under a treated net	Residual	Dermal	Child	Chronic	NA
R-LLIN-7	Sleeping under a treated net	Residual	Dermal	Toddler	Chronic	NA
R-LLIN-8	Sleeping under a treated net	Residual	Dermal	Infant	Chronic	NA
R-LLIN-9	Sleeping under a treated net	Residual	Oral (hand-to-mouth)	Toddler	Chronic	NA
R-LLIN-10	Sleeping under a treated net	Residual	Oral (hand-to-mouth)	Infant	Chronic	NA
R-LLIN-11	Sleeping under a treated net	Residual	Oral (direct)	Toddler	Chronic	NA
R-LLIN-12	Sleeping under a treated net	Residual	Oral (direct)	Infant	Chronic	NA
R-LLIN-13	Sleeping under a treated net	Residual	Oral (breast milk)	Infant	Chronic	NA
R-LLIN-14	Contact while washing nets	Liquid	Dermal	Adult woman	Chronic	NA
R-LLIN-15	Contact while washing nets	Liquid	Dermal	Child	Chronic	NA
R-LLIN-16	Contact while washing nets	Liquid	Oral (hand-to-mouth)	Adult woman	Chronic	NA
R-LLIN-17	Contact while washing nets	Liquid	Oral (hand-to-mouth)	Child	Chronic	NA
R-LLIN-18	Contact while washing nets	Liquid	Oral (breast milk)	Infant	Chronic	NA
R-LLIN-19	Contact while washing nets	Liquid	Dermal	Adult woman	Acute	NA
R-LLIN-20	Contact while washing nets	Liquid	Dermal	Child	Acute	NA
R-LLIN-21	Contact while washing nets	Liquid	Oral (hand-to-mouth)	Adult woman	Acute	NA
R-LLIN-22	Contact while washing nets	Liquid	Oral (hand-to-mouth)	Child	Acute	NA

Table F1-3. Hammock Scenarios

ID	Exposure Scenarios	Type	Exposure Route	Receptor	Exposure	Safety
Resident Scenarios						
R-Hamm-	Sleeping on hammock	Residual	Dermal	Adult woman	Chronic	NA
R-Hamm-	Sleeping on hammock	Residual	Dermal	Child	Chronic	NA
R-Hamm-	Sleeping on hammock	Residual	Dermal	Toddler	Chronic	NA
R-Hamm-	Sleeping on hammock	Residual	Dermal	Infant	Chronic	NA
R-Hamm-	Sleeping on hammock	Residual	Oral (hand-to-mouth)	Toddler	Chronic	NA
R-Hamm-	Sleeping on hammock	Residual	Oral (hand-to-mouth)	Newborn	Chronic	NA
R-Hamm-	Sleeping on hammock	Residual	Oral (direct)	Toddler	Chronic	NA
R-Hamm-	Sleeping on hammock	Residual	Oral (direct)	Infant	Chronic	NA
R-Hamm-	Sleeping on hammock	Residual	Oral (breast milk)	Infant	Chronic	NA
R-Hamm-	Contact while washing treated	Liquid	Dermal	Adult woman	Chronic	NA
R-Hamm-	Contact while washing treated	Liquid	Dermal	Child	Chronic	NA
R-Hamm-	Contact while washing treated	Liquid	Oral (hand-to-mouth)	Adult woman	Chronic	NA
R-Hamm-	Contact while washing treated	Liquid	Oral (hand-to-mouth)	Child	Chronic	NA
R-Hamm-	Contact while washing treated	Liquid	Oral (breast milk)	Infant	Chronic	NA
R-Hamm-	Contact while washing treated	Liquid	Dermal	Adult woman	Acute	NA
R-Hamm-	Contact while washing treated	Liquid	Dermal	Child	Acute	NA
R-Hamm-	Contact while washing treated	Liquid	Oral (hand-to-mouth)	Adult woman	Acute	NA
R-Hamm-	Contact while washing treated	Liquid	Oral (hand-to-mouth)	Child	Acute	NA

Table F1-4. Larviciding Scenarios

ID	Exposure Scenarios	Type	Exposure Route	Receptor	Exposure	Safety
Worker/Operator Scenarios						
W-Larv-1	Mixing/loading of larvicide	Liquid	Dermal	Adult woman	Chronic	Guidelines
W-Larv-2	Mixing/loading of larvicide	Liquid	Dermal	Adult woman	Chronic	Lax (No PPE)
W-Larv-3	Spray application	Liquid	Dermal	Adult woman	Chronic	Guidelines
W-Larv-4	Spray application	Liquid	Dermal	Adult woman	Chronic	Lax (No PPE)
Resident Scenarios						
R-Larv-1	Contact with larvicide treated	Residual	Oral	Adult woman	Chronic	NA
R-Larv-2	Contact with larvicide treated	Residual	Oral	Child	Chronic	NA
R-Larv-3	Contact with larvicide treated	Residual	Oral	Toddler	Chronic	NA
R-Larv-4	Contact with larvicide treated	Residual	Dermal	Adult woman	Chronic	NA
R-Larv-5	Contact with larvicide treated	Residual	Dermal	Child	Chronic	NA
R-Larv-6	Contact with larvicide treated	Residual	Dermal	Toddler	Chronic	NA
R-Larv-7	Contact with larvicide treated	Residual	Dermal	Infant	Chronic	NA
R-Larv-8	Contact with larvicide treated	Residual	Breast milk	Infant	Chronic	NA

ANNEX F2: EXPOSURE AND RISK CALCULATIONS

TABLE F2-I. GENERAL FORM OF THE RISK EQUATIONS

$$\text{SysDose} = [\text{C}] \times [\text{CR}] \times \left[\frac{\text{ABS} \times \cdots}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
C	Concentration in media [mg a.i./*x*], where *x* is a unit for quantifying the media (e.g. m^2 for insecticide loading on a treated net)
CR	Contact rate with media [*x*/d], where *x* is the same unit as in the denominator of *C*
ABS	Absorption factor, the fraction of dose absorbed by the receptor [*unitless*]
…	Additional multipliers representing various sources of dose attenuation or concentration [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [*y*/*z*], where *y* and *z* can be any units describing the frequency of occurrence (e.g., d/yr, operations/d)
ED	Exposure duration [*z*], where *z* is the same unit as in the denominator of *EF*
AT	Averaging time [*y*], where *y* is the same unit as in the numerator of *EF*

Note that C may be a "concentration" in terms of mg a.i. per volume (e.g. mg/L), area (e.g. mg/m^2), or mass (e.g. mg/kg). The numerator of *CR* is always in the same unit as the denominator of *C*, such that the product *C* × *CR* (the *exposure*) is in units of mg a.i./d.

The final term *EF* × *ED* / *AT* (sometimes called the "exposure factor") is a unitless multiplier used to amortize the dose over time. When exposure is continuous (occurring every day for one or more days), this factor equals 1. Otherwise it represents the fraction of days during which exposure occurs over a specified period. To obtain the "lifetime average daily dose" used in cancer risk calculations, AT is set to the length of the receptor's life. When calculating the hazard quotient, the period of time represented by ED and AT is identical because adverse effects are evaluated only during the period of exposure.

C and *CR* are often the result of additional calculations. In subsequent tables, brackets are placed as above to clarify the variables used to derive each term and shading is used to identify groups of variables pertaining to each bracket.

TABLE F2-II. HAZARD QUOTIENT

$$HQ = \frac{SysDose}{RfD}$$	
HQ	Hazard quotient [*unitless*]
SysDose	Average daily dose [mg a.i./kg/d]
RfD	Reference dose, i.e. the dose to which a receptor may be exposed with no adverse effects expected [mg a.i./kg/d]

Acute, chronic, or subchronic HQ may be calculated depending on the exposure duration used to compute *SysDose* (ED<1 month, 1<ED<6 months, or ED>6 months, respectively) by selecting the corresponding *RfD*.

TABLE F2-III. INCREMENTAL CANCER RISK

$$ILCR = LADD \times SF$$	
ILCR	Lifetime incremental cancer risk, i.e. the incremental risk of developing cancer from the calculated lifetime dose [*unitless*]
LADD	Lifetime average daily dose, i.e. the average daily dose amortized over the receptor's life span [mg a.i./kg/d]
SF	Slope factor, a quantity representing the relationship between dose and cancer incidence [$(mg\ a.i./kg/d)^{-1}$]

TABLE F2-1A. SCENARIOS W-IRS-1–6:
INDOOR RESIDUAL SPRAYING, MIXING/LOADING AND SPRAYING, WORKER EXPOSURE

$$\text{SysDose} = \left[\text{TC}_{\text{wall}} \times \text{UE} \times \text{CF}_{\text{kg/mg}}\right] \times \left[SA_{wall} \times \text{SR}\right] \times \left[\frac{\text{ABS} \times \text{PF}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
TC_{wall}	Target concentration of a.i. on the wall [mg/m^2]
UE	Unit exposure, activity-specific (mixing/loading powder, mixing/loading emulsifiable concentrate, spraying) [mg a.i./kg a.i.]
$CF_{kg/mg}$	Conversion factor [kg/mg]
SA_{wall}	Surface area of treated walls [m^2/house]
SR	Spray rate [house/d]
ABS	Dermal or inhalation absorption factor, depending on exposure route [*unitless*]
PF	Protection factor from PPE [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-1B. SCENARIOS R-IRS-1–3
INDOOR RESIDUAL SPRAYING, POST-APPLICATION, RESIDENTS, DERMAL EXPOSURE

$$\text{SysDose} = [\text{TC}_{\text{wall}} \times \text{F}_{\text{effective}} \times \text{F}_{\text{avail}} \times \text{F}_{\text{trans}}] \times [\text{SA}_{IRS}] \times \left[\frac{\text{ABS}_{\text{dermal}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
TC_{wall}	Target concentration on the wall [mg a.i./m^2]
$F_{effective}$	Adjustment factor representing variable a.i. concentrations and contact rates for floor versus walls [*unitless*]
F_{avail}	Average fraction of residue available for contact over exposure duration [*unitless*]
F_{trans}	Fraction of residue available for transfer [*unitless*]
SA_{IRS}	Skin surface area contacting IRS treated area per day [m^2/d]
ABS_{dermal}	Dermal absorption factor [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-1C. SCENARIO R-IRS-4
INDOOR RESIDUAL SPRAYING, POST-APPLICATION, TODDLER, HAND-TO-MOUTH EXPOSURE

$$\text{SysDose} = [\text{TC}_{\text{wall}} \times \text{F}_{\text{effective}} \times \text{F}_{\text{avail}} \times \text{F}_{\text{trans}}] \times [\text{SA}_{hands}] \times \left[\frac{\text{ABS}_{\text{oral}} \times \text{TE}_{\text{h2m}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
TC_{wall}	Target concentration on the wall [mg a.i./m^2]
$F_{effective}$	Adjustment factor representing variable a.i. concentrations and contact rates for floor versus walls [*unitless*]
F_{avail}	Average fraction of residue available for contact over exposure duration [*unitless*]
F_{trans}	Fraction of residue available for transfer [*unitless*]
SA_{hands}	Hand surface area contacting IRS treated area per day [m^2/d]
ABS_{oral}	Oral absorption factor [*unitless*]
TE_{h2m}	Transfer efficiency from hand to mouth for toddler [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-1D. SCENARIO R-IRS-5–8
INDOOR RESIDUAL SPRAYING, POST-APPLICATION, RESIDENTS, INHALATION EXPOSURE

$$\text{SysDose} = \left[\frac{\text{VP} \times \text{MW} \times \text{CF}_{\text{mg/g}}}{R \times \text{T} \times \text{AER}}\right] \times \left[\text{BR} \times \text{T}_{\text{indoors}}\right] \times \left[\frac{\text{ABS}_{\text{resp}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
VP	Vapor pressure of the a.i. [Pa]
MW	Molecular weight of the a.i. [g/mol]
$CF_{mg/g}$	Conversion factor [mg/g]
R	Ideal gas constant [$Pa \cdot m^3/(K \cdot mol)$]
T	Ambient temperature [K]
AER	Air exchange rate, in number of exchanges per day [*unitless*]
BR	Hourly breathing rate [m^3/hr]
$T_{indoors}$	Time spent indoors [hr/d]
ABS_{resp}	Respiratory absorption factor [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-1E. SCENARIO R-IRS-9
INDOOR RESIDUAL SPRAYING, POST-APPLICATION, INFANT, BREAST MILK EXPOSURE

$$\text{SysDose} = \left[\text{Dose}_{\text{mother}} \times \frac{T_{1/2}}{\ln 2} \times \text{BF}\right] \times [\text{IR}] \times \left[\frac{\text{ABS}_{\text{oral}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
$\text{Dose}_{\text{mother}}$	Average daily dose of the mother [mg a.i./kg/d]
$T_{1/2}$	Half-life of a.i. in the body [d]
BF	Breast milk concentration factor [*unitless*]
IR	Ingestion rate of breast milk [kg/d]
ABS_{oral}	Oral absorption factor [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-2A. SCENARIO R-LLIN-1–4
LONG-LASTING INSECTICIDAL NETS, SLEEPING, RESIDENTS, INHALATION EXPOSURE

$$\text{SysDose} = \left[\frac{\text{VP} \times \text{MW} \times \text{CF}_{\text{mg/g}}}{R \times \text{T} \times \text{AER}}\right] \times \left[\text{BR}_{\text{sleep}} \times \text{T}_{\text{sleep}}\right] \times \left[\frac{\text{ABS}_{\text{resp}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
VP	Vapor pressure of the a.i. [Pa]
MW	Molecular weight of the a.i. [g/mol]
$CF_{mg/g}$	Conversion factor [mg/g]
R	Ideal gas constant [Pa·m^3/(K·mol)]
T	Ambient temperature [K]
AER	Air exchange rate, in number of exchanges per day [*unitless*]
BR_{sleep}	Hourly breathing rate while sleeping [m^3/hr]
T_{sleep}	Sleep duration [hr/d]
ABS_{resp}	Respiratory absorption factor [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-2B. SCENARIO R-LLIN-5–8
LONG-LASTING INSECTICIDAL NETS, SLEEPING, RESIDENTS, DERMAL EXPOSURE

$$\text{SysDose} = [\text{TC}_{\text{net}} \times \text{F}_{\text{trans}}] \times [\text{SA}_{net}] \times \left[\frac{\text{ABS}_{\text{dermal}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
TC_{net}	Target concentration of a.i. on the net [mg/m^2]
F_{trans}	Fraction of residue available for transfer [*unitless*]
SA_{net}	Skin surface area in contact with the net during sleep [m^2/d]
ABS_{dermal}	Dermal absorption factor [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-2C. SCENARIO R-LLIN-9–10
LONG-LASTING INSECTICIDAL NETS, SLEEPING, TODDLER/INFANT, HAND-TO-MOUTH EXPOSURE

$$\text{SysDose} = [\text{TC}_{\text{net}} \times \text{F}_{\text{trans}}] \times [\text{SA}_{hands}] \times \left[\frac{\text{ABS}_{\text{oral}} \times \text{TE}_{\text{h2m}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
TC_{net}	Target concentration of a.i. on the net [mg/m^2]
F_{trans}	Fraction of residue available for transfer [*unitless*]
SA_{hands}	Hand surface area contacting net per day [m^2/d]
ABS_{oral}	Oral absorption factor [*unitless*]
TE_{h2m}	Transfer efficiency from hand to mouth for toddler/infant [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-2D. SCENARIO R-LLIN-11–12
LONG-LASTING INSECTICIDAL NETS, SLEEPING, TODDLER/INFANT, DIRECT ORAL EXPOSURE

$$\text{SysDose} = [\text{TC}_{\text{net}} \times \text{F}_{\text{trans}}] \times [\text{CR}_{\text{mouth}}] \times \left[\frac{\text{ABS}_{\text{oral}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
TC_{net}	Target concentration of a.i. on the net [mg/m^2]
$F_{release}$	Fraction of residue available for release during oral exposure [*unitless*]
CR_{mouth}	Surface area of net mouthed during sleep [m^2/d]
ABS_{oral}	Oral absorption factor [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]
AT	Averaging time [d]

TABLE F2-2E. SCENARIO R-LLIN-13, 18
LONG-LASTING INSECTICIDAL NETS, MULTIPLE SCENARIOS, INFANT, BREAST MILK EXPOSURE

$$\text{SysDose} = \left[\text{Dose}_{\text{mother}} \times \frac{\text{T}_{1/2}}{\ln 2} \times \text{BF}\right] \times [\text{IR}] \times \left[\frac{\text{ABS}_{\text{oral}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
$\text{Dose}_{\text{mother}}$	Average daily dose of the mother [mg a.i./kg/d]
$\text{T}_{1/2}$	Half-life of a.i. in the body [d]
BF	Breast milk concentration factor [*unitless*]
IR	Ingestion rate of breast milk [kg/d]
ABS_{oral}	Oral absorption factor [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-2F. SCENARIO R-LLIN-14–15, 19–20
LONG-LASTING INSECTICIDAL NETS, WASHING, ADULT/CHILD, DERMAL EXPOSURE TO WASH WATER

$$\text{SysDose} = \left[\frac{\text{TC}_{\text{net}} \times \text{A}_{\text{net}} \times \text{F}_{\text{release}}}{\text{V}_{\text{wash}} \times \text{CF}_{\text{mL/L}}}\right] \times [\text{CR}_{\text{skin}}] \times \left[\frac{\text{ABS}_{\text{dermal}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
TC_{net}	Target concentration of a.i. on the net [mg/m^2]
A_{net}	Area of the net [m^2]
$F_{release}$	Fraction of residue available for release during washing [*unitless*]
V_{wash}	Wash water volume [L]
$CF_{mL/L}$	Conversion factor [mL/L]
CR_{skin}	Volume of water contacting skin during wash [mL/d]
ABS_{dermal}	Dermal absorption factor [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

Note: [EF × ED / AT] term is omitted when computing acute exposure.

TABLE F2-2G. SCENARIO R-LLIN-16–17, 21–22
LONG-LASTING INSECTICIDAL NETS, WASHING, ADULT/CHILD, HAND-TO-MOUTH EXPOSURE TO WASH WATER

$$\text{SysDose} = \left[\frac{\text{TC}_{\text{net}} \times \text{A}_{\text{net}} \times \text{F}_{\text{release}}}{\text{V}_{\text{wash}} \times \text{CF}_{\text{mL/L}}}\right] \times [\text{CR}_{\text{hands}}] \times \left[\frac{\text{ABS}_{\text{oral}} \times \text{TE}_{\text{h2m}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
TC_{net}	Target concentration of a.i. on the net [mg/m^2]
A_{net}	Area of the net [m^2]
$F_{release}$	Fraction of residue available for release during washing [*unitless*]
V_{wash}	Wash water volume [L]
$CF_{mL/L}$	Conversion factor [mL/L]
CR_{hands}	Volume of water contacting hands during wash [mL/d]
ABS_{oral}	Oral absorption factor [*unitless*]
TE_{h2m}	Transfer efficiency from hand to mouth [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

Note: [EF × ED / AT] term is omitted when computing acute exposure.

TABLE F2-3A. SCENARIO R-HAMM-1–4
HAMMOCKS, SLEEPING, RESIDENTS, DERMAL EXPOSURE

$$\text{SysDose} = [\text{TC}_{\text{hamm}} \times \text{F}_{\text{trans}}] \times [\text{SA}_{hamm}] \times \left[\frac{\text{ABS}_{\text{dermal}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
TC_{hamm}	Target concentration of a.i. on the hammock [mg/m^2]
F_{trans}	Fraction of residue available for transfer [*unitless*]
SA_{hamm}	Skin surface area in contact with the hammock during sleep [m^2/d]
ABS_{dermal}	Dermal absorption factor [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-3B. SCENARIO R-HAMM-5–6
HAMMOCKS, SLEEPING, TODDLER/INFANT, HAND-TO-MOUTH EXPOSURE

$$\text{SysDose} = [\text{TC}_{\text{hamm}} \times \text{F}_{\text{trans}}] \times [\text{SA}_{hands}] \times \left[\frac{\text{ABS}_{\text{oral}} \times \text{TE}_{\text{h2m}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
TC_{hamm}	Target concentration of a.i. on the hammock [mg/m^2]
F_{trans}	Fraction of residue available for transfer [*unitless*]
SA_{hands}	Hand surface area contacting hammock per day [m^2/d]
ABS_{oral}	Oral absorption factor [*unitless*]
TE_{h2m}	Transfer efficiency from hand to mouth [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-3C. SCENARIO R-HAMM-7–8
HAMMOCKS, SLEEPING, TODDLER/INFANT, DIRECT ORAL EXPOSURE

$$\text{SysDose} = [\text{TC}_{\text{hamm}} \times \text{F}_{\text{release}}] \times [\text{CR}_{\text{mouth}}] \times \left[\frac{\text{ABS}_{\text{oral}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
TC_{hamm}	Target concentration of a.i. on the hammock [mg/m^2]
$F_{release}$	Fraction of residue available for release during oral exposure [*unitless*]
CR_{mouth}	Surface area of hammock mouthed during sleep [m^2/d]
ABS_{oral}	Oral absorption factor [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-3D. SCENARIO R-HAMM-9, 14
HAMMOCKS, MULTIPLE SCENARIOS, INFANT, BREAST MILK EXPOSURE

$$\text{SysDose} = \left[\text{Dose}_{\text{mother}} \times \frac{T_{1/2}}{\ln 2} \times \text{BF}\right] \times [\text{IR}] \times \left[\frac{\text{ABS}_{\text{oral}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
$\text{Dose}_{\text{mother}}$	Average daily dose of the mother [mg a.i./kg/d]
$T_{1/2}$	Half-life of a.i. in the body [d]
BF	Breast milk concentration factor [*unitless*]
IR	Ingestion rate of breast milk [kg/d]
ABS_{oral}	Oral absorption factor [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-3E. SCENARIO R-HAMM-10–11, 15–16
HAMMOCKS, WASHING, ADULT/CHILD, DERMAL EXPOSURE TO WASH WATER

$$\text{SysDose} = \left[\frac{\text{TC}_{\text{hamm}} \times \text{A}_{\text{hamm}} \times \text{F}_{\text{release}}}{\text{V}_{\text{wash}} \times \text{CF}_{\text{mL/L}}}\right] \times [\text{CR}_{\text{skin}}] \times \left[\frac{\text{ABS}_{\text{dermal}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
TC_{hamm}	Target concentration of a.i. on the hammock [mg/m^2]
A_{hamm}	Area of the hammock [m^2]
$F_{release}$	Fraction of residue available for release during washing [*unitless*]
V_{wash}	Wash water volume [L]
$CF_{mL/L}$	Conversion factor [mL/L]
CR_{skin}	Volume of water contacting skin during wash [mL/d]
ABS_{dermal}	Dermal absorption factor [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

Note: [EF × ED / AT] term is omitted when computing acute exposure.

TABLE F2-3F. SCENARIO R-HAMM-12–13, 17–18
HAMMOCKS, WASHING, ADULT/CHILD, HAND-TO-MOUTH EXPOSURE TO WASH WATER

$$\text{SysDose} = \left[\frac{\text{TC}_{\text{hamm}} \times \text{A}_{\text{hamm}} \times \text{F}_{\text{release}}}{\text{V}_{\text{wash}} \times \text{CF}_{\text{mL/L}}}\right] \times [\text{CR}_{\text{hands}}] \times \left[\frac{\text{ABS}_{\text{oral}} \times \text{TE}_{\text{h2m}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
TC_{hamm}	Target concentration of a.i. on the hammock [mg/m^2]
A_{hamm}	Area of the hammock [m^2]
$F_{release}$	Fraction of residue available for release during washing [*unitless*]
V_{wash}	Wash water volume [L]
$CF_{mL/L}$	Conversion factor [mL/L]
CR_{hands}	Volume of water contacting hands during wash [mL/d]
ABS_{oral}	Oral absorption factor [*unitless*]
TE_{h2m}	Transfer efficiency from hand to mouth [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

Note: [EF × ED / AT] term is omitted when computing acute exposure.

TABLE F2-4A. SCENARIO W-LARV-1–4
LARVICIDE, MIXING/LOADING AND SPRAYING, WORKER EXPOSURE

$$\text{SysDose} = \left[\text{TC}_{\text{water area}} \times \text{UE} \times \text{CF}_{\text{kg/mg}}\right] \times \left[\text{SR}_{\text{water area}}\right] \times \left[\frac{\text{ABS}_{\text{dermal}} \times \text{PF}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
$TC_{water\ area}$	Target areal concentration of a.i. applied to the water surface [mg/m^2]
UE	Unit exposure, activity-specific (mixing/loading vs. spraying) [mg a.i./kg a.i.]
$CF_{kg/mg}$	Conversion factor [kg/mg]
$SR_{water\ area}$	Water surface area treated per day [m^2/d]
ABS_{dermal}	Dermal absorption factor [unitless]
PF	Protection factor from PPE [unitless]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-4B. SCENARIO R-LARV-1–3
LARVICIDE, GROUND WATER EXPOSURE, RESIDENTS, INGESTION

$$\text{SysDose} = [\text{TC}_{\text{water area}} \times \text{SG}] \times [\text{WIR} \times \text{CF}_{\text{m3/L}}] \times \left[\frac{\text{ABS}_{\text{oral}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
$TC_{water\ area}$	Target areal concentration of a.i. applied to the water surface [mg/m^2]
SG	Concentration factor calculated from the SCI-GROW model, based on a.i. K_{oc} and half-life in the soil [m^2/m^3]
WIR	Water ingestion rate [L/d]
$CF_{m3/L}$	Conversion factor [m^3/L]
ABS_{oral}	Oral absorption factor [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-4C. SCENARIO R-LARV-4–7
LARVICIDE, GROUND WATER EXPOSURE, RESIDENTS, DERMAL

$$\text{SysDose} = [\text{TC}_{\text{water area}} \times \text{SG}] \times [\text{FT} \times \text{SA}_{\text{body}}] \times \left[\frac{\text{ABS}_{dermal}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

$$\text{AF} = \max\left(1, \frac{\text{T}_{1/}}{\ln 2 \times \text{TI}}\right)$$

SysDose	Average daily dose [mg a.i./kg/d]
$TC_{water\ area}$	Target areal concentration of a.i. applied to the water surface [mg/m^2]
SG	Concentration factor calculated from the SCI-GROW model, based on a.i. K_{oc} and half-life in the soil [m^2/m^3]
FT	Film thickness of liquid in contact with immersed body [m]
SA_{body}	Body surface area contact rate [m^2/d]
ABS_{dermal}	Dermal absorption factor [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

TABLE F2-4D. SCENARIO R-LARV-8
LARVICIDE, GROUND WATER EXPOSURE, INFANT, BREAST MILK EXPOSURE

$$\text{SysDose} = \left[\text{Dose}_{\text{mother}} \times \frac{\text{T}_{1/2}}{\ln 2} \times \text{BF}\right] \times [\text{IR}] \times \left[\frac{\text{ABS}_{\text{oral}}}{\text{BW}}\right] \times \left[\frac{\text{EF} \times \text{ED}}{\text{AT}}\right]$$

SysDose	Average daily dose [mg a.i./kg/d]
$\text{Dose}_{\text{mother}}$	Average daily dose of the mother [mg a.i./kg/d]
$\text{T}_{1/2}$	Half-life of a.i. in the body [d]
BF	Breast milk concentration factor [*unitless*]
IR	Ingestion rate of breast milk [kg/d]
ABS_{oral}	Oral absorption factor [*unitless*]
BW	Body weight [kg]
EF	Exposure frequency [d/yr]
ED	Exposure duration [yr]
AT	Averaging time [d]

ANNEX F3: INPUT VARIABLE VALUES

Indoor Residual Spray Input Data

Intervention	Worker (W-IRS-1-8)	Resident (R-IRS-1-3)	Resident (R-IRS-4)	Resident (R-IRS-5-8)	Resident (R-IRS-9)	Variable Name	Variable	Units	Value	Reference
IRS						Dose	SysDose	mg a.i./kg bw-day	Calculated	Calculated
IRS						Dose mother	Dosemother	mg a.i./kg bw-day	Calculated	Calculated
IRS						Unit exposure -mixing/loading - dermal - WP formula	UEmix_WP	mg a.i./kg a.i.	8.2	EPA, 2015
IRS						Unit exposure -mixing/loading - dermal - EC formula	UEmix_EC	mg a.i./kg a.i.	0.49	EPA, 2015
IRS						Unit exposure -mixing/loading - dermal – WP-SB formula	UEmix_WPSB	mg a.i./kg a.i.	0	EPA, 2015
IRS						Unit exposure -mixing/loading - dermal - SC formula	UEmix_SC	mg a.i./kg a.i.	0.49	EPA, 2015
IRS						Unit exposure -mixing/loading - dermal - CS formula	UEmix_CS	mg a.i./kg a.i.	0	EPA, 2015
IRS						Unit exposure - spraying - inhalation	UEspr_inhal	mg a.i./kg a.i.	0.066	EPA, 2015
IRS						Unit exposure - spraying - dermal	UEspr_derm	mg a.i./kg a.i.	5.5	EPA, 2015
IRS						Target concentration	TCwall	mg a.i./m2	Per a.i.	See a.i. table
IRS						Conversion factor	CFkg/mg	kg/mg	1.00E-06	
IRS						Spray rate	SR	house/day	11	Survey data
IRS						Protection factor from PPE - mixing/loading - Solid	PFmix_solid	Unitless	0.02	PEA, 2012

Intervention	Worker (W-IRS-1-8)	Resident (R-IRS-1-3)	Resident (R-IRS-4)	Resident (R-IRS-5-8)	Resident (R-IRS-9)	Variable Name	Variable	Units	Value	Reference
						formulations				
IRS						Protection factor from PPE - mixing/loading - Liquid formulations	PFmix_Liquid	Unitless	0.03	Machera et al., 2009
IRS						Protection factor from PPE - spraying - inhalation	PFspr_inhal	Unitless	0.05	Machera et al., 2009
IRS						Protection factor from PPE - Spraying - dermal	PFspr_derm	Unitless	0.023	Machera et al., 2009
IRS						Dermal absorption factor	ABSdermal	Unitless	Per a.i.	EPA, 2004
IRS						Respiratory absorption factor	ABSresp	Unitless	Per a.i.	EPA, 2004
IRS						Oral absorption factor	ABSoral	Unitless	Per a.i.	EPA, 2004
IRS						Body weight - adult	BW	kg	62	WHO GRAM IRS, 2011
IRS						Body weight - child	BWchild	kg	32	WHO GRAM IRS, 2011; EPA, 2012
IRS						Body weight - toddler	BWtoddler	kg	14	WHO GRAM IRS, 2011; EPA, 2012
IRS						Body weight - infant	BWinfant	kg	4.8	WHO GRAM IRS, 2011
IRS						Exposure frequency - Worker	EF	days/yr	72	2012 PEA
IRS						Exposure frequency - Resident	EF	days/yr	365	2012 PEA
IRS						Exposure duration	ED	years	1	2012 PEA
IRS						Averaging Time	AT	days	365	2012 PEA
IRS						Surface area of treated walls	SAwall	m2/house	35.8	World Bank 1996
IRS						Hourly breathing rate	BR	m3/hr	0.89 (adult) 0.90 (child) 1.00 (toddler) 0.66 (infant)	EPA, 2012 Default values for “light activity”

Intervention	Worker (W-IRS-1-8)	Resident (R-IRS-1-3)	Resident (R-IRS-4)	Resident (R-IRS-5-8)	Resident (R-IRS-9)	Variable Name	Variable	Units	Value	Reference
IRS						Time spent indoors	Tindoors	hr/day	12	Assumption, 2012 PEA
IRS						Fraction of insecticide available for contact	Favail	Unitless	0.42	WHO GRAM IRS, 2011
IRS						Fraction translodged onto skin	Ftrans	Unitless	0.14	EPA, 2012
IRS						Transfer efficiency from hand to mouth for toddler	TEh2m	Unitless	0.1	WHO GRAM IRS, 2011
IRS						First order kinetics half-life in the mother	T ½ mother	days	Per a.i.	See a.i. table
IRS						Ingestion rate of breast milk	IRmilk	kg/day	0.95	WHO GRAM IRS, 2011
IRS						Adjustment factor for variable a.i. conc.; contact rates for floor vs. walls	Feffective	Unitless	0.15	WHO GRAM IRS, 2011
IRS						Skin surface area contacting IRS treated area per day	SAirs	m2/day	0.204 (adult) 0.191 (child) 0.376 (toddler)	WHO GRAM IRS, 2011
IRS						Hand surface area contacting IRS treated area per day	SAhands	m2/day	0.032	WHO GRAM IRS, 2011
IRS						Vapor pressure	VP	Pa	Per a.i.	See a.i. table
IRS						Air exchanges per day	AER	Unitless	24	WHO GRAM IRS, 2011
IRS						Molecular weight	MW	g/mol	Per a.i.	See a.i. table
IRS						Conversion factor (mg/g)	CFmg/g	mg/g	1000	
IRS						Ideal gas law constant	R	Pa-m3/K-mol	8.314	
IRS						Ambient temperature	T	K	298	WHO GRAM IRS, 2011; EPA, 2012
IRS						Breast milk concentration	BF	Unitless	1.19 ($pK_{ow} < 2$)	WHO GRAM IRS, 2011

Intervention	Worker (W-IRS-1-8)	Resident (R-IRS-1-3)	Resident (R-IRS-4)	Resident (R-IRS-5-8)	Resident (R-IRS-9)	Variable Name	Variable	Units	Value	Reference
						factor			0.25 (pK_{ow} ≥2)	
IRS						Octanol-water partition coefficient	pKow	Unitless	Per a.i.	See a.i. table

Indoor Residual Spray Input Data by Active Ingredient

Industry Name	Active Ingredient	TCwall	ABSdermal	ABSresp	ABSoral	T 1/2mother	VP	MW	pKow
		mg ai/m2	Unitless	Unitless	Unitless	days	Pa	g/mol	Unitless
Phantom	chlorfenapyr 240 SC	250	0.1 (ac) 0.05 (ch)	1	1	2.33	5.40E-06	407.6	4.83
Sumishield	clothianidin	300	0.1	1	1	30	1.31E-07	249.68	0.7
Fludora Fusion	clothianidin	200	0.1	1	1	30	1.31E-07	249.68	0.7
Fludora Fusion	deltamethrin	25	0.1	1	1	30	1.20E-07	505.24	5.43
Pirimiphos-methyl	pirimiphos-methyl	1500	0.1	1	1	1	2.00E-03	305.3	4.12
Actellic 300CS	pirimiphos-methyl	1000	0.1	1	1	1	2.00E-03	305.3	4.12
alpha-cypermethrin	alpha-cypermethrin	25	0.1 (ac) 0.025 (ch)	1	1	18.24	7.83E-05	416.3	6.94
bendiocarb	bendiocarb	250.00	0.1	1	1	30	4.60E-03	223.23	1.70
bifenthrin	bifenthrin	37.5	0.1	1	1	30	2.40E-05	422.87	6.00
chlorfenapyr	chlorfenapyr	400	0.1	1	1	2.33	5.40E-06	407.6	4.83
cyfluthrin	cyfluthrin	35	0.1	1	1	1	2.10E-08	434.29	5.95
DDT	DDT	1500	0.03	1	1	287	2.13E-05	354.49	6.91
deltamethrin	deltamethrin	22.5	0.1	1	1	30	1.20E-07	505.24	5.43
etofenprox	etofenprox	200	0.1	1	1	30	8.13E-07	376.5	7.05
fenitrothion	fenitrothion	2000	0.1	1	1	30	1.57E-03	277.24	3.30
lambda-cyhalothrin	lambda-cyhalothrin	25	0.1	1	1	30	2.00E-07	449.9	7.00
malathion	malathion	2000	0.1	1	1	1	5.29E-03	330.36	2.36
propoxur	propoxur	1500	0.1	1	1	30	1.29E-03	209.24	1.52

Worker (W-IRS-1-8) Mixing/loading of solid or liquid formulations, spraying mixed solutions. Dermal and inhalation exposure with IRS insecticide for workers

Resident (R-IRS-1-3) Dermal exposure post-application for resident

Resident (R-IRS-4) Hand-to-mouth exposure post-application for toddler

Resident (R-IRS-5-8) Inhalation exposure to IRS insecticide - post application (for insecticides with VP >3.75E-07 mm/Hg) for residents

Resident (R-IRS-9) Breast milk exposure post-application for infant

IRS References for Chemical-Specific Values

TCwall References for DDT, malathion, fenitrothion, Pirimiphos-methyl, bendiocarb, propoxur, alpha-cypermethrin, bifenthrin, cyfluthrin, deltamethrin, etofenprox, and lambda-cyhalothrin: WHO recommended insecticides for indoor residual spraying against malaria vectors. 2 March 2015. Available at: http://www.who.int/whopes/Insecticides_IRS_2_Mar_2015.pdf.

TCwall References for Chlorfenapyr 240 SC: 16th WHOPES Working Group Meeting, 22-30 July 2013; 17th WHOPES Working Group meeting, 15-19 September 2014. Available at: http://who.int/whopes/resources/en/

TCwall References for Clothianidin: SumiShield (http://sumivector.com/irs/sumishield-50wg); Fludora Fusion (personal communication).

ABSdermal: The default ABS of 0.1 is taken from Exhibit 3-4 of EPA's Dermal Risk Assessment Guidance for Superfund (EPA 2004) and pertains to absorption of semivolatile organic compounds from a solid medium (soil). Chemical-specific ABS values are referenced in Annex D3, with the exception of DDT which is taken from Exhibit 3-4 of EPA (2004).

T1/2 mother references:

Default value of 30 set for half-life in the mother when data was not available (expert judgment).

Alpha-cypermethrin: BASF, 2014

Chlorfenapyr: BASF, 2014

Cyfluthrin: ATSDR (2003). Toxicological Profile for Pyrethrins and Pyretrhoids. Available at: http://www.atsdr.cdc.gov/toxprofiles/tp155.pdf

DDT: Bouwman, H., Kylin, H., Sereda, B. and Bornman, R. (2012). High levels of DDT in breast milk: Intake, risk, lactation duration, and involvement of gender. Environmental Pollution 170: 63-70. Available at: https://www.diva-portal.org/smash/get/diva2:564144/FULLTEXT01.pdf

Malathion: National Pesticide Information Center Fact Sheet on Malathion. Available at: http://npic.orst.edu/factsheets/malagen.html

Pirimiphos-methyl: Wolterink, G. and Moretto, A. (2006). Pirimiphos-Methyl. WHO JMPR monograph. Available at: http://apps.who.int/pesticide-residues-jmpr-database/pesticide?name=PIRIMIPHOS-METHYL.

VP, MW, pKow references: see Annex D1

Long-Lasting Insecticide Net Input Data

Intervention	Resident (R-LLIN-1-4)	Resident (R-LLIN-5-8)	Resident (R-LLIN-9-10)	Resident (R-LLIN-11-12)	Resident (R-LLIN-13, 18)	Resident (R-LLIN-14-17)	Resident (R-LLIN-19-22)	Variable Name	Variable	Units	Value	Reference
LLIN								Dose	SysDose	mg a.i./kg bw-day	Calculated	Calculated
LLIN								Dose mother	Dosemother	mg a.i./kg bw-day	Calculated	Calculated
LLIN								Target concentration	TCnet	mg a.i./kg	Per a.i.	See a.i. table
LLIN								Area of the net	Anet	m^2	15	Najera & Zaim 2002
LLIN								Dermal absorption factor	ABSdermal	Unitless	Per a.i.	EPA, 2004
LLIN								Respiratory absorption factor	ABSresp	Unitless	Per a.i.	EPA, 2004
LLIN								Oral absorption factor	ABSoral	Unitless	Per a.i.	EPA, 2004
LLIN								Body weight	BW	kg	62	WHO GRAM NETS, 2012
LLIN								Body weight - child	BWchild	kg	32	WHO GRAM NETS, 2012; EPA, 2012
LLIN								Body weight - toddler	BWtoddler	kg	14	WHO GRAM NETS, 2012; EPA, 2012
LLIN								Body weight - infant	BWinfant	kg	4.8	WHO GRAM NETS, 2012
LLIN								Exposure frequency	EF	days/yr	365	
LLIN								Exposure frequency	EFwash	days/yr	20/3	WHO GRAM NETS, 2012
LLIN								Exposure duration - chronic noncancer risk	EDnoncarc	years	1	

Intervention	Resident (R-LLIN-1-4)	Resident (R-LLIN-5-8)	Resident (R-LLIN-9-10)	Resident (R-LLIN-11-12)	Resident (R-LLIN-13, 18)	Resident (R-LLIN-14-17)	Resident (R-LLIN-19-22)	Variable Name	Variable	Units	Value	Reference
LLIN								Exposure duration - cancer risk	EDcarc	years	39 (adult) 5 (child) 5 (toddler) 1 (infant)	
LLIN								Averaging Time - chronic noncancer risk	AT	days	365	2012 PEA
LLIN								Averaging Time - cancer risk	AT	days	18250	2012 PEA
LLIN								Surface area in contact with net during sleep	SAnet	m2/day	0.41 (adult) 0.25 (child) 0.15 (toddler) 0.070 (infant)	WHO GRAM NETS, 2012
LLIN								Hourly breathing rate while sleeping	BRsleep	m3/hr	0.4 (adult) 0.38 (child, toddler) 0.28 (infant)	WHO GRAM NETS, 2012
LLIN								Time spent sleeping	Tsleep	hr/day	9 (adult) 10 (child) 12 (toddler) 14 (infant)	WHO GRAM NETS, 2012
LLIN								Fraction translodged onto skin	Ftrans	Unitless	0.06	WHO GRAM NETS, 2012
LLIN								Transfer efficiency from hand to mouth	TEh2m	Unitless	0.1	WHO GRAM NETS, 2012

Intervention	Resident (R-LLIN-1-4)	Resident (R-LLIN-5-8)	Resident (R-LLIN-9-10)	Resident (R-LLIN-11-12)	Resident (R-LLIN-13, 18)	Resident (R-LLIN-14-17)	Resident (R-LLIN-19-22)	Variable Name	Variable	Units	Value	Reference
LLIN								First order kinetics half-life in the mother	T ½ mother	days	Per a.i.	See a.i. table
LLIN								Ingestion rate of breast milk	IRmilk	kg/day	0.95	WHO GRAM NETS, 2012
LLIN								Hand surface area contacting LLIN per day	SAhands	m2/day	0.032 (toddler) 0.015 (infant)	WHO GRAM NETS, 2012
LLIN								Vapor pressure	VP	Pa	Per a.i.	See a.i. table
LLIN								Air exchanges per day	AER	Unitless	24	WHO GRAM NETS, 2012
LLIN								Molecular weight	MW	g/mol	Per a.i.	See a.i. table
LLIN								Conversion factor (mg/g)	CFmg/g	mg/g	1000	
LLIN								Ideal gas law constant	R	Pa-m3/K-mol	8.314	
LLIN								Ambient temperature	T	K	298	WHO GRAM NETS, 2012
LLIN								Breast milk concentration factor	BF	Unitless	1.19 ($pK_{ow} < 2$) 0.25 ($pK_{ow} \geq 2$)	WHO GRAM NETS, 2012
LLIN								Octanol-water partition coefficient	pKow	Unitless	Per a.i.	See a.i. table
LLIN								Fraction of residue available for release during oral exposure	Frelease	Unitless	0.33	WHO GRAM NETS, 2012
LLIN								Surface area of net mouthed during sleep	CRmouth	m2/day	0.005	WHO GRAM NETS, 2012

Intervention	Resident (R-LLIN-1-4)	Resident (R-LLIN-5-8)	Resident (R-LLIN-9-10)	Resident (R-LLIN-11-12)	Resident (R-LLIN-13, 18)	Resident (R-LLIN-14-17)	Resident (R-LLIN-19-22)	Variable Name	Variable	Units	Value	Reference
LLIN								Wash water volume	Vwash	L	4	WHO GRAM NETS, 2012
LLIN								Conversion factor (mL/L)	CFmL/L	mL/L	1000	
LLIN								Volume of water contacting skin during wash	CRskin	mL/day	36 (adult) 20 (child)	WHO GRAM NETS, 2012
LLIN								Volume of water contacting hands during wash	CRhands	mL/day	9.3 (adult) 5.4 (child)	WHO GRAM NETS, 2012

Resident (R-LLIN-1-4) Inhalation exposure from sleeping under treated net (all receptors)
Resident (R-LLIN-5-8) Dermal exposure from sleeping under treated net for resident
Resident (R-LLIN-9-10) Hand-to-mouth oral exposure for toddler and infant-resident
Resident (R-LLIN-11-12) Direct oral exposure with treated net for toddler and infant-resident
Resident (R-LLIN-13, 18) Breast milk exposure for infant-resident
Resident (R-LLIN-14-17) Washing of nets - Dermal exposure to insecticide in wash water for adult, child resident
Resident (R-LLIN-19-22) Washing of nets - Hand-to-mouth exposure to insecticide in water water for adult, child resident

Long-Lasting Insecticide Net Input Data by Active Ingredient

Industry Name	Active Ingredient	Tcnet	ABSdermal	ABSresp	ABSoral	T 1/2mother	VP	MW	pKow
		mg/m^2	Unitless	Unitless	Unitless	Days	Pa	g/mol	Unitless
Interceptor G2	alpha-cypermethrin	100	0.1 (ac) 0.025 (ch)	1	1	18.24	7.83E-05	416.3	6.94
Interceptor G2	chlorfenapyr	200	0.1 (ac) 0.05 (ch)	1	1	2.33	5.40E-06	407.6	4.83
Royal Guard	alpha-cypermethrin	225	0.1 (ac) 0.025 (ch)	1	1	18.24	7.83E-05	416.3	6.94
Royal Guard	pyriproxyfen	225	0.1	1	1	30	1.33E-05	321.4	5.37
Royal Sentry	alpha-cypermethrin	261	0.1 (ac) 0.025 (ch)	1	1	18.24	7.83E-05	416.3	6.94
Olyset Duo	permethrin	800	0.1	1	1	1	6.90E-06	391.3	6.5
Olyset Duo	pyriproxifen	400	0.1	1	1	30	1.33E-05	321.4	5.37
Olyset Plus	permethrin	800	0.1	1	1	1	6.90E-06	391.3	6.5
Olyset Plus	piperonyl butoxide	400	0.1	1	1	30	2.11E-05	338.4	4.75
Panda Net 2.0	deltamethrin	76	0.1	1	1	30	1.20E-07	505.24	5.43
DuraNet	alpha-cypermethrin	247.5	0.1 (ac) 0.025 (ch)	1	1	18.24	7.83E-05	416.3	6.94
DawaPlus	deltamethrin	85	0.1	1	1	30	1.20E-07	505.24	5.43
Permanet 3.0	deltamethrin	85	0.1	1	1	30	1.20E-07	505.24	5.43
Permanet 3.0	piperonyl butoxide	200	0.1	1	1	30	2.11E-05	338.4	4.75
Olyset	permethrin	1000	0.1	1	1	1	6.90E-06	391.3	6.5
ICON-MAXX	lambda cyhalothrin	50	0.1	1	1	30	2.00E-07	449.9	7.00
ITN	alpha-cypermethrin	40	0.1 (ac) 0.025 (ch)	1	1	18.24	7.83E-05	416.3	6.94
ITN	cyfluthrin	50	0.1	1	1	1	2.10E-08	434.29	5.95
ITN	deltamethrin	25	0.1	1	1	30	1.20E-07	505.24	5.43
ITN	etofenprox	200	0.1	1	1	30	8.13E-07	376.5	7.05
ITN	lambda	15	0.1	1	1	30	2.00E-07	449.9	7.00

Industry Name	Active Ingredient	Tcnet	ABSdermal	ABSresp	ABSoral	T 1/2mother	VP	MW	pKow
	cyhalothrin								
ITN	permethrin	500	0.1	1	1	1	6.90E-06	391.3	6.5

LLIN References for Chemical-Specific Values

TCnet references:

Interceptor G2: Beigel, C. (2014). Evaluation of potential exposure to alphacypermethrin (BAS 310 I) and related health risk associated to the use of Interceptor G2 long lasting impregnated mosquito nets. BASF DocID No. 2014/1233167.

Beigel, C. (2014). Evaluation of potential exposure to chlorfenapyr (BAS 306 I) and related health risk associated to the use of Interceptor G2 long lasting impregnated mosquito nets (LLIN). BASF DocID No. 2014/1233166.

Royal Guard: personal communication

Royal Sentry: WHOPES, 2013. Alpha-cypermethrin: Long-lasting (incorporated into filaments) insecticidal nets. Available at: http://www.who.int/whopes/quality/en/Alphacypermethrin_WHO_specs_eval_Jan_2013.pdf

Olyset Duo: Active ingredient target concentration: Ohashi, K. and Shono, Y. (2015). Recent Progress in the Research and Development of New Products for Malaria and Dengue Vector Control. Sumitomo Chemical Co., Ltd. Available at: https://www.sumitomo-chem.co.jp/english/rd/report/theses/docs/2015E_1.pdf . Weight of the net: Olyset Plus Technical Brochure Available at: http://sumivector.com/sites/default/files/site-content/pdf/Olyset_Plus_Technical_Brochure_Jan_2013_ENG.pdf

Olyset Plus: Olyset Plus Technical Brochure Available at: http://sumivector.com/sites/default/files/site-content/pdf/Olyset_Plus_Technical_Brochure_Jan_2013_ENG.pdf

Panda Net 2.0: WHOPES, 2015. Report of the 18th WHOPES Working Group Meeting. http://apps.who.int/iris/bitstream/10665/184034/1/9789241509428_eng.pdf?ua=1

DuraNet: DuraNet Specification Sheet, Available at: http://duranetllin.com/specifications/

DawaPlus: DawaPlus Specification Sheet, Available at:

Permanet 3.0: Permanet 3.0 Technical Brochure, Available at: http://www.vestergaard.com/images/pdf/PN3_Tech_Eng_2015.pdf

Olyset: Olyset Net Specification Sheet. Available at: www.sumivector.com

ICON-MAXX: ICON-MAXX Product Leaflet, Available at: http://www3.syngenta.com/eame/PPM/SiteCollectionDocuments/Leaflets/Vector_control/Icon_Maxx_Marketing_Leaflet/Icon_Maxx_English.pdf

ABSdermal: The default ABS of 0.1 is taken from Exhibit 3-4 of EPA's Dermal Risk Assessment Guidance for Superfund (EPA 2004) and pertains to absorption of semivolatile organic compounds from a solid medium (soil). Chemical-specific ABS values are referenced in Annex D3.

T1/2 mother references:

Default value of 30 set for half-life in the mother when data was not available (expert judgment).
Alpha-cypermethrin: BASF, 2014
Chlorfenapyr: BASF, 2014
Cyfluthrin: ATSDR (2003). Toxicological Profile for Pyrethrins and Pyretrhoids. Available at: http://www.atsdr.cdc.gov/toxprofiles/tp155.pdf
Permethrin: ATSDR, 2009.

VP, MW, pKow references: see Annex D1

Spinosad: EMA, 2011

Hammock Data Inputs

Intervention	Resident (R-Hamm-1-4)	Resident (R-Hamm-5-6)	Resident (R-Hamm-7-8)	Resident (R-Hamm-9, 14)	Resident (R-Hamm-10-13)	Resident (R-Hamm-15-18)	Variable Name	Variable	Units	Value	Reference
Hammock							Dose	SysDose	mg a.i./kg bw-day	Calculated	Calculated
Hammock							Dose mother	Dosemother	mg a.i./kg bw-day	Calculated	Calculated
Hammock							Target concentration	TChamm	mg a.i./m2	Per a.i.	See a.i. table
Hammock							Area of hammock	Ahamm	m2	2.13	PLoS One 4(10):e7369 (2009) Thang et al.
Hammock							Dermal absorption factor	ABSdermal	Unitless	Per a.i.	EPA, 2004
Hammock							Oral absorption factor	ABSoral	Unitless	Per a.i.	EPA, 2004
Hammock							Body weight	BW	kg	62	WHO GRAM NETS, 2012
Hammock							Body weight - child	BWchild	kg	32	WHO GRAM NETS, 2012
Hammock							Body weight - toddler	BWtoddler	kg	14	WHO GRAM NETS, 2012
Hammock							Body weight - infant	BWinfant	kg	4.8	WHO GRAM NETS, 2012
Hammock							Exposure frequency	EF	days/yr	365	
Hammock							Exposure frequency	EFwash	days/yr	20/3	WHO GRAM NETS, 2012
Hammock							Exposure duration - chronic noncancer risk	EDnoncarc	years	1	
Hammock							Exposure duration - cancer risk	EDcarc	years	39 (adult) 5 (child) 5 (toddler)	

Intervention	Resident (R-Hamm-1-4)	Resident (R-Hamm-5-6)	Resident (R-Hamm-7-8)	Resident (R-Hamm-9, 14)	Resident (R-Hamm-10-13)	Resident (R-Hamm-15-18)	Variable Name	Variable	Units	Value	Reference
										1 (infant)	
Hammock							Averaging Time - chronic noncancer risk	AT	days	365	2012 PEA
Hammock							Averaging Time - cancer risk	AT	days	18250	EPA, 2012
Hammock							Surface area in contact with hammock during sleep	SAhamm	m2/day	0.85 (adult) 0.54 (child) 0.31 (toddler) 0.15 (infant)	1/2 total body area, per EPA 2012 guideline for mattresses
Hammock							Fraction translodged onto skin	Ftrans	Unitless	0.06	WHO GRAM NETS, 2012
Hammock							Transfer efficiency from hand to mouth for toddler	TEh2m	Unitless	0.1	WHO GRAM NETS, 2012
Hammock							First order kinetics half-life in the mother	T 1/2 mother	days	Per a.i.	See a.i. table
Hammock							Ingestion rate of breast milk	IRmilk	kg/day	0.95	WHO GRAM NETS, 2012
Hammock							Hand surface area contacting hammock per day	SAhands	m2/day	0.032 (toddler) 0.015 (infant)	WHO GRAM NETS, 2012
Hammock							Breast milk concentration factor	BF	Unitless	1.19 ($pK_{ow} < 2$) 0.25 ($pK_{ow} \geq 2$)	WHO GRAM NETS, 2012
Hammock							Octanol-water partition coefficient	pKow	Unitless	Per a.i.	See a.i. table

Intervention	Resident (R-Hamm-1-4)	Resident (R-Hamm-5-6)	Resident (R-Hamm-7-8)	Resident (R-Hamm-9, 14)	Resident (R-Hamm-10-13)	Resident (R-Hamm-15-18)	Variable Name	Variable	Units	Value	Reference
Hammock							Fraction of residue available for release during oral exposure	Frelease	Unitless	0.33	WHO GRAM NETS, 2012
Hammock							Surface area of hammock mouthed during sleep	CRmouth	m2/day	0.005	WHO GRAM NETS, 2012
Hammock							Wash water volume	Vwash	L	4	WHO GRAM NETS, 2012
Hammock							Conversion factor (mL/L)	CFmL/L	mL/L	1000	
Hammock							Volume of water contacting skin during wash	CRskin	mL/day	36 (adult) 20 (child)	WHO GRAM NETS, 2012
Hammock							Volume of water contacting hands during wash	CRhands	mL/day	9.3 (adult) 5.4 (child)	WHO GRAM NETS, 2012

Resident (R-Hamm-1-4) Dermal exposure from sleeping on treated hammock
Resident (R-Hamm-5-6) Hand-to-mouth oral exposure for toddler and infant
Resident (R-Hamm-7-8) Direct oral exposure with treated hammock for toddler and infant
Resident (R-Hamm-9, 14) Breast milk exposure for infant
Resident (R-Hamm-10-13) Washing of hammocks - Dermal exposure to insecticide in wash water for adult, child
Resident (R-Hamm-15-18) Washing of hammocks - Hand-to-mouth exposure to insecticide in wash water for adult, child

Hammock Data Inputs by Active Ingredient

Active Ingredient	TChamm	ABSdermal	ABSoral	T 1/2mother	pKow
	(mg/m^2)	Unitless	Unitless	days	Unitless
deltamethrin	80	0.1	1	30	5.43
permethrin	1500	0.1	1	1	6.5

Hammock References for Chemical-Specific Values

TChamm, permethrin: Rozendaal, J.A. (1997). Vector control: Methods used by individuals and communities. World Health Organization. Available at:
WHO, 2000. Control Measures, Chapter 1. Mosquitos and Other Biting Diptera. Available at:
http://www.who.int/water_sanitation_health/resources/vector007to28.pdf.

TChamm, deltamethrin, assumed same active ingredient target concentration as PandaNet 2.0: WHOPES, 2015. Report of the 18th WHOPES Working Group Meeting. http://apps.who.int/iris/bitstream/10665/184034/1/9789241509428_eng.pdf?ua=1

ABSdermal: The default ABS of 0.1 is taken from Exhibit 3-4 of EPA's Dermal Risk Assessment Guidance for Superfund (EPA 2004) and pertains to absorption of semivolatile organic compounds from a solid medium (soil).

T1/2 mother reference, permethrin: ATSDR, 2009.

pKow reference: see Annex D1

Larvicide Data Inputs

Intervention	Worker (W-Larv-1-4)	Resident (R-Larv-1-3)	Resident (R-Larv-4-7)	Resident (R-Larv-8)	Variable Name	Variable	Units	Value	Reference
Larvicide					Dose	SysDose	mg a.i./kg bw-day	Calculated	Calculated
Larvicide					Dose mother	Dosemother	mg a.i./kg bw-day	Calculated	Calculated
Larvicide					Unit exposure - mixing/loading -dermal - WP formula	UEmix_WP	mg a.i./kg a.i.	8.2	EPA, 2015
Larvicide					Unit exposure - mixing/loading -dermal - EC formula	UEmix_EC	mg a.i./kg a.i.	0.49	EPA, 2015
Larvicide					Unit exposure - mixing/loading -dermal - SC formula	UEmix_SC	mg a.i./kg a.i.	0.49	EPA, 2015
Larvicide					Unit exposure - mixing/loading -dermal - G formula	UEmix_G	mg a.i./kg a.i.	0.02	EPA, 2015
Larvicide					Unit exposure - mixing/loading -dermal - DT formula	UEmix_DT	mg a.i./kg a.i.	0.02	EPA, 2015
Larvicide					Unit exposure - spraying	UEspray	mg a.i./kg a.i.	18.21	EPA, 2012
Larvicide					Target application rate	TCwater area	mg a.i./m2	Per a.i.	See a.i. table
Larvicide					Conversion factor	CFkg/mg	kg/mg	1.00E-06	

Intervention	Worker (W-Larv-1-4)	Resident (R-Larv-1-3)	Resident (R-Larv-4-7)	Resident (R-Larv-8)	Variable Name	Variable	Units	Value	Reference
Larvicide					Water surface area treated per day	SRwater area	m2/day	390	2012 PEA
Larvicide					Protection factor from PPE - mixing/loading - Solid formuations	PFmix	Unitless	0.02	2012 PEA
Larvicide					Protection factor from PPE - mixing/loading - Liquid formulations	PFmix	Unitless	0.03	Machera et al., 2009
Larvicide					Protection factor from PPE - spraying - dermal	PFspray	Unitless	0.023	Machera et al., 2009
Larvicide					Dermal absorption factor	ABSdermal	Unitless	Per a.i.	See a.i. table
Larvicide					Oral absorption factor	ABSoral	Unitless	Per a.i.	See a.i. table
Larvicide					Body weight	BW	kg	62	WHO GRAM larv, 2011
Larvicide					Body weight - child	BWchild	kg	32	WHO GRAM larv, 2011
Larvicide					Body weight - toddler	BWtoddler	kg	14	WHO GRAM larv, 2011
Larvicide					Body weight - infant	BWinfant	kg	4.8	WHO GRAM larv, 2011
Larvicide					Exposure frequency - Worker	EF	days/yr	156	WHO GRAM larv, 2011
Larvicide					Exposure frequency - Resident	EF	days/yr	365	WHO GRAM larv, 2011

Intervention	Worker (W-Larv-1-4)	Resident (R-Larv-1-3)	Resident (R-Larv-4-7)	Resident (R-Larv-8)	Variable Name	Variable	Units	Value	Reference
Larvicide					Exposure duration- chronic noncancer risk	ED	years	1	WHO GRAM larv, 2011
Hammock					Exposure duration - cancer risk	EDcarc	years	39 (adult) 5 (child) 5 (toddler) 1 (infant)	
Larvicide					Averaging Time	AT	days	365	2012 PEA
Larvicide					Half-life of a.i. in water	T 1/2	days	Per a.i.	See a.i. table
Larvicide					Ingestion rate of breast milk	IRmilk	kg/day	0.95	WHO GRAM larv, 2011
Larvicide					Breast milk concentration factor	BF	Unitless	1.19 (pKow < 2); 0.25 (pKow ≥2)	WHO GRAM larv, 2011
Larvicide					Octanol-water partition coefficient	pKow	Unitless	Per a.i.	See a.i. table
Larvicide					SCI-GROW concentration factor	SG	m2/m3	Calcuated	Calculated
Larvicide					Water ingestion rate	WIR	L/day	2 (adults) 1 (child/toddler)	WHO GRAM larv, 2011
Larvicide					Film thickness of liquid in contact with immersed body	FT	m	0.0001	WHO GRAM larv, 2011

Intervention	Worker (W-Larv-1-4)	Resident (R-Larv-1-3)	Resident (R-Larv-4-7)	Resident (R-Larv-8)	Variable Name	Variable	Units	Value	Reference
Larvicide					Body surface area contact rate	SAbody	m2/day	1.69 (adult) 1.08 (child) 0.610 (toddler) 0.290 (infant)	WHO GRAM larv, 2011
Larvicide					First order kinetics half time AI in the body	T 1/2mother	day	Per a.i.	See a.i. table
Larvicide					Conversion factor	CFm3/L	m3/L	0.001	

Worker (W-Larv-1-4) Mixing/loading of liquid formulations, spraying and mixed solutions - Direct dermal exposure with larvicide for workers
Resident (R-Larv-1-3) Ingestion of treated groundwater
Resident (R-Larv-4-7) Dermal exposure to treated groundwater during bathing
Resident (R-Larv-8) Breast milk exposure for infant

Larvicide Data Inputs by Active Ingredient

Industry Name	Active Ingredient	TC water area	ABSdermal	ABSoral	T 1/2 water	T 1/2 soil	T 1/2 mother	Koc	pKow
		mg/m2	Unitless	Unitless	days	days	days	ml/g	Unitless
	chlorpyrifos	2.50	0.1	1	24.5	42	30	15998	4.96
Dimilin	diflubenzuron	10.00	0.1 (ac) 0.005 (ch)	1	180	14	30	8695	3.89
Fenthion	fenthion	11.20	0.2 (ac) 0.03 (ch)	1	21.1	34	30	2700	4.09
Altosid	methoprene	3.00	0.1	1	13	10	30	23000	5.5
Novaluron 10%	novaluron 10%	10.00	0.1	1	101	31.3	30	8929	5.27
Pirimiphos-methyl 300 CS	pirimiphos-methyl	50.00	0.1	1	79	5.6	1	4725	4.12
Sumilarv 0.5	pyriproxyfen	5.00	0.1	1	7.5	12.4	30	405000	5.37
Spinosad	spinosad	50.00	n/a	1	30	17.3	2	35838	4.01
Spinosad 83.3 monolayer	spinosad 83.3 monolayer	50.00	n/a	1	30	17.3	2	35838	4.01
Spinosad 25 extended release	spinosad 25 extended release	40.00	n/a	1	30	17.3	2	35838	4.01
Abate, ProVect	temephos	11.20	0.38	1	17.2	30.0	30	25025	5.96

Larvicide References for Chemical-Specific Values

Note: Chemical health effect risks are not quantified for *Bacillus thuringiensis*, and therefore are not presented in this table.
n/a: not applicable, dermal pathway is not assessed (spinosad) or exposure was qualitatively assessed (*Bacillus thuringiensis*).

Larvicide application rate reference: WHOPES, 2013. WHOPES-recommended compounds and formulations for control of mosquito larvae. Available at: http://www.who.int/whopes/Mosquito_Larvicides_25_Oct_2013.pdf. When a range of application rates was provided, the upper bound was used in the risk calculations.

ABSdermal: The default ABS of 0.1 is taken from Exhibit 3-4 of EPA's Dermal Risk Assessment Guidance for Superfund (EPA 2004) and pertains to absorption of semivolatile organic compounds from a solid medium (soil). Chemical-specific ABS values are referenced in Annex D3.

T1/2 mother references:

Default value of 30 set for half-life in the mother when data was not available (expert judgment).

Pirimiphos-methyl: Wolterink, G. and Moretto, A. (2006). Pirimiphos-Methyl. WHO JMPR monograph. Available at: http://apps.who.int/pesticide-residues-jmpr-database/pesticide?name=PIRIMIPHOS-METHYL.

Spinosad: EMA, 2011

Half-life soil, Half-life water, Koc, and pKow references: see Annex D1

ANNEX G: WORKED EXAMPLES OF THE HUMAN HEALTH RISK ASSESSMENT PROCESS

Example G1: Chronic Hazard Quotient, Indoor Residual Spraying, Post-application, Toddler (Scenarios R-IRS-3, 4, and 7)

There are three IRS post-application exposure scenarios for the Toddler receptor: dermal exposure via contact with walls, oral exposure via hand-mouth contacts, and inhalation exposure due to volatilized a.i. Here, risk calculations for these scenarios are illustrated for the IRS product Phantom, which contains active ingredient chlorfenapyr 240 SC.

First, average daily dose (ADD) is calculated for each exposure scenario. The following sections walk through the calculations, using equations and data inputs from Annexes G-2 and G-3, respectively.

Average Daily Dose – Dermal Exposure

Parameters for this calculation include:

PARAMETER	VALUE	EXPLANATION
TC_{wall}	250 mg a.i./m^2	Target concentration on the wall, obtained from product information.
$F_{effective}$	0.15 [*unitless*]	Adjustment factor representing variable a.i. concentrations and contact rates for floor versus walls. Follows WHO GRAM recommendations, which are based on assumptions that (1) the floor is incidentally contaminated with IRS in a 50-cm strip around the house perimeter, at 30% of TC_{wall}, and (2) 10% of the receptor's contacts are with the walls, and the remaining 90% with the floor.
F_{avail}	0.42 [*unitless*]	Average fraction of residue available for contact over exposure duration. Follows WHO GRAM recommendations, which are based on first order decay over a 6-month period, with half-life of 60 d.
F_{trans}	0.14 [*unitless*]	Fraction of residue available for transfer. The value is the recommended default for treated paints and preservatives given by EPA SOPs (2012).
SA_{IRS}	0.376 m^2/d	Skin surface area contacting IRS treated area per day. Follows WHO GRAM recommendations, which vary by receptor. For the toddler receptor in this example, it is assumed that the daily skin surface area coming into contact with treated surfaces is equal to the total area of head, hands, arms, legs, and feet.
ABS_{dermal}	0.05 [*unitless*]	Dermal absorption factor. This is a product-specific value.
BW	14 kg	Body weight. This is the default value recommended by the WHO GRAM.
EF	365 d/yr	Exposure frequency. The calculated exposure is assumed to occur daily.

PARAMETER	VALUE	EXPLANATION
ED	1 yr	Exposure duration. The chronic risk of exposure is considered over a one-year period.
AT	365 d	Averaging time. The value is set to compute ADD over a 1-yr period.

Plugging into the equation for ADD yields:

$$SysDose_{dermal} = \left[TC_{wall} \times F_{effective} \times F_{avail} \times F_{trans}\right] \times \left[SA_{IRS}\right] \times \left[\frac{ABS_{dermal}}{BW}\right] \times \left[\frac{EF \times ED}{AT}\right]$$

$$SysDose_{dermal} = \left[250\,\frac{mg\ a.i.}{m^2} \times 0.15 \times 0.42 \times 0.14\right] \times \left[0.376\,\frac{m^2}{d}\right] \times \left[\frac{0.05}{14\ kg}\right] \times \left[\frac{365\,\frac{d}{yr} \times 1\ yr}{365\ d}\right]$$

$$SysDose_{dermal} = \left[2.2\,\frac{mg\ a.i.}{m^2}\right] \times \left[0.376\,\frac{m^2}{d}\right] \times \left[0.0036\,\frac{1}{kg}\right] \times [1]$$

$$SysDose_{dermal} = 0.0029\,\frac{mg\ a.i.}{kg \cdot d}$$

Average Daily Dose – Hand-mouth Exposure

Parameters for this calculation include:

Parameter	Value	Explanation
TC_{wall}	250 mg a.i./m^2	Target concentration on the wall, obtained from product information.
$F_{effective}$	0.15 [*unitless*]	Adjustment factor representing variable a.i. concentrations and contact rates for floor versus walls. Follows WHO GRAM recommendations, which are based on assumptions that (1) the floor is incidentally contaminated with IRS in a 50-cm strip around the house perimeter, at 30% of TC_{wall}, and (2) 10% of the receptor's contacts are with the walls, and the remaining 90% with the floor.
F_{avail}	0.42 [*unitless*]	Average fraction of residue available for contact over exposure duration. Follows WHO GRAM recommendations, which are based on first order decay over a 6-month period, with half-life of 60 d.
F_{trans}	0.14 [*unitless*]	Fraction of residue available for transfer. The value is the recommended default for "treated paints and preservatives" given by EPA SOPs (2012).

Parameter	Value	Explanation
SA_{hands}	0.032 m^2/d	Hand surface area contacting IRS treated area per day. Follows WHO GRAM recommendations, which assumes that the complete skin surface area of the hands contacts contaminated surfaces daily.
ABS_{oral}	1.0 [*unitless*]	Oral absorption factor. This is the default value recommended by the WHO GRAM.
TE_{h2m}	0.1 [*unitless*]	Transfer efficiency from hand to mouth for toddler. This is the default value recommended by the WHO GRAM.
BW	14 kg	Body weight. This is the default value recommended by the WHO GRAM.
EF	365 d/yr	Exposure frequency. The calculated exposure is assumed to occur daily.
ED	1 yr	Exposure duration. The chronic risk of exposure is considered over a one-year period.
AT	365 d	Averaging time. The value is set to compute ADD over a 1-yr period.

Plugging into the equation for ADD yields:

$$SysDose_{h-m} = \left[TC_{wall} \times F_{effective} \times F_{avail} \times F_{trans}\right] \times \left[SA_{hands}\right] \times \left[\frac{ABS_{oral} \times TE_{h2m}}{BW}\right] \times \left[\frac{EF \times ED}{AT}\right]$$

$$SysDose_{h-m} = \left[250\,\frac{mg\ a.i.}{m^2} \times 0.15 \times 0.42 \times 0.14\right] \times \left[0.032\,\frac{m^2}{d}\right] \times \left[\frac{1.0 \times 0.1}{14\,kg}\right] \times \left[\frac{365\,\frac{d}{yr} \times 1\,yr}{365\,d}\right]$$

$$SysDose_{h-m} = \left[2.2\,\frac{mg\ a.i.}{m^2}\right] \times \left[0.032\,\frac{m^2}{d}\right] \times \left[0.0071\,\frac{1}{kg}\right] \times [1]$$

$$SysDose_{h-m} = 0.00050\,\frac{mg\ a.i.}{kg \cdot d}$$

Average Daily Dose – Inhalation Exposure

Parameters for this calculation include:

Parameter	Value	Explanation
VP	5.4e-6 Pa	Vapor pressure of the a.i., obtained from product information or MSDS.
MW	407.6 g/mol	Molecular weight of the a.i., obtained from product information or MSDS.
$CF_{mg/g}$	1000 mg/g	Conversion factor.
R	8.314 Pa·m^3/(K·mol)	Ideal gas constant.
T	298 K	Ambient temperature, equivalent to 25 °C (77 °F). This is the default value recommended by the WHO GRAM.
AER	24	Air exchange rate, in number of exchanges per day [*unitless*]
BR	1.00 m^3/hr	Hourly breathing rate. Follows WHO GRAM recommendations, which vary by receptor and activity level. This is the default value for adult receptors undergoing "light activity."
$T_{indoors}$	12 hr/d	Time spent indoors. This is the default value recommended by the WHO GRAM.
ABS_{resp}	1 [*unitless*]	Respiratory absorption factor. This is the default value recommended by the WHO GRAM, which conservatively assumes that 100% of inhaled a.i. is absorbed.
BW	14 kg	Body weight. This is the default value recommended by the WHO GRAM.
EF	365 d/yr	Exposure frequency. The calculated exposure is assumed to occur daily.
ED	1 yr	Exposure duration. The chronic risk of exposure is considered over a one-year period.
AT	365 d	Averaging time. The value is set to compute ADD over a 1-yr period.

Plugging into the equation for ADD yields:

$$SysDose_{inhal} = \left[\frac{VP \times MW \times CF_{mg/g}}{R \times T \times AER}\right] \times [BR \times T_{indoors}] \times \left[\frac{ABS_{resp}}{BW}\right] \times \left[\frac{EF \times ED}{AT}\right]$$

$$SysDose_{inhal} = \left[\frac{5.4 \cdot 10^{-6}\ Pa\ \times\ 407.6\,\frac{g}{mol}\ \times\ 1000\,\frac{mg}{g}}{8.314\,\frac{Pa \cdot m^3}{K \cdot mol}\ \times\ 298\,K\ \times\ 24}\right] \times \left[1.00\,\frac{m^3}{hr}\ \times\ 12\,\frac{hr}{d}\right] \times \left[\frac{1}{14\ kg}\right] \times \left[\frac{365\,\frac{d}{yr}\ \times\ 1\ yr}{365\ d}\right]$$

$$SysDose_{inhal} = \left[0.000037\,\frac{mg}{m^3}\right] \times \left[12\,\frac{m^3}{d}\right] \times \left[0.071\,\frac{1}{kg}\right] \times [1]$$

$$SysDose_{inhal} = 0.000032\,\frac{mg\ a.i.}{kg \cdot d}$$

Chronic Hazard Quotients

The hazard quotient (HQ) for each exposure scenario is computed by dividing ADD by the appropriate reference dose (RfD) from Annex D. The total HQ for the receptor is the sum of the HQs for all scenarios.

$$HQ_{dermal} = \frac{0.0029\,\frac{mg\ a.i.}{kg \cdot d}}{0.026\,\frac{mg\ a.i.}{kg \cdot d}} = 0.11$$

$$HQ_{h-m} = \frac{0.00050\,\frac{mg\ a.i.}{kg \cdot d}}{0.026\,\frac{mg\ a.i.}{kg \cdot d}} = 0.019$$

$$HQ_{inhal} = \frac{0.000032\,\frac{mg\ a.i.}{kg \cdot d}}{0.026\,\frac{mg\ a.i.}{kg \cdot d}} = 0.0012$$

$$HQ_{total} = HQ_{dermal} + HQ_{h-m} + HQ_{inhal} = 0.11 + 0.019 + 0.0012 = \mathbf{0.13}$$

Example G2: Chronic Hazard Quotient, Long-lasting Insecticidal Nets, Sleeping, Adult (Scenarios R-LLIN-1 and 5)

There are two exposure scenarios for the Adult receptor sleeping under an LLIN: dermal exposure via contact with the LLIN, and inhalation exposure due to volatilized a.i. Here, risk calculations for these scenarios are illustrated for the LLIN product Olyset Duo, which contains two active ingredients: permethrin and pyriproxyfen. Risk is calculated separately for the two a.i., and summed at the end to yield total risk for the product.

First, average daily dose (ADD) is calculated for each exposure scenario. The following sections walk through the calculations, using equations and data inputs from Annexes G-2 and G-3, respectively.

Average Daily Dose – Dermal Exposure

Parameters for this calculation include:

Parameter	Value	Explanation
TC_{net}	800 mg a.i./m^2 (permethrin) 400 mg a.i./m^2 (pyriproxyfen)	Target concentration of a.i. on the net, obtained from product information.
F_{trans}	0.06 [*unitless*]	Fraction of residue available for transfer. The value is the recommended default for impregnated textiles or carpeting given by EPA SOPs (2012).
SA_{net}	0.41 m^2/d	Skin surface area in contact with the net during sleep. Follows WHO GRAM recommendation, which assumes that the skin surface area coming into contact with an LLIN during one night of sleep is equal to one third of the total area of trunk, hands, arms, lower legs, and feet.
ABS_{dermal}	0.1 [*unitless*]	Dermal absorption factor. This is the default value recommended by the WHO GRAM.
BW	62 kg	Body weight. This is the default value recommended by the WHO GRAM.
EF	365 d/yr	Exposure frequency. The calculated exposure is assumed to occur daily.
ED	1 yr	Exposure duration. The chronic risk of exposure is considered over a one-year period.
AT	365 d	Averaging time. The value is set to compute ADD over a 1-yr period.

Plugging the permethrin values into the equation for ADD yields:

$$SysDose_{dermal,permethrin} = [TC_{net} \times F_{trans}] \times [SA_{net}] \times \left[\frac{ABS_{dermal}}{BW}\right] \times \left[\frac{EF \times ED}{AT}\right]$$

$$SysDose_{dermal,permethrin} = \left[800\,\frac{mg\ a.i.}{m^2} \times 0.06\right] \times \left[0.41\,\frac{m^2}{d}\right] \times \left[\frac{0.1}{62\ kg}\right] \times \left[\frac{365\,\frac{d}{yr} \times 1\ yr}{365\ d}\right]$$

$$SysDose_{dermal,permethrin} = \left[48\,\frac{mg\ a.i.}{m^2}\right] \times \left[0.41\,\frac{m^2}{d}\right] \times \left[0.0016\,\frac{1}{kg}\right] \times [1]$$

$$SysDose_{dermal,permethrin} = 0.032\,\frac{mg\ a.i.}{kg{\cdot}d}$$

For pyriproxyfen, the same equation yields:

$$SysDose_{dermal,pyriproxyfen} = 0.016\,\frac{mg\ a.i.}{kg{\cdot}d}$$

Average Daily Dose – Inhalation Exposure

Parameters for this calculation include:

Parameter	Value	Explanation
VP	6.90E-6 Pa (permethrin) 1.33E-5 Pa (pyriproxyfen)	Vapor pressure of the a.i., obtained from product information or MSDS.
MW	391.3 g/mol (permethrin) 321.4 g/mol (pyriproxyfen)	Molecular weight of the a.i., obtained from product information or MSDS.
$CF_{mg/g}$	1000 mg/g	Conversion factor.
R	8.314 Pa·m^3/(K·mol)	Ideal gas constant.

Parameter	Value	Explanation
T	298 K	Ambient temperature, equivalent to 25 °C (77 °F). This is the default value recommended by the WHO GRAM.
AER	24	Air exchange rate, in number of exchanges per day [*unitless*]
BR_{sleep}	0.4 m^3/hr	Hourly breathing rate. Follows WHO GRAM recommendations, which vary by receptor and activity level. This is the default value for adult receptors while sleeping.
T_{sleep}	9 hr/d	Sleep duration. This is the default value recommended by the WHO GRAM.
ABS_{resp}	1 [*unitless*]	Respiratory absorption factor. This is the default value recommended by the WHO GRAM, which conservatively assumes that 100% of inhaled a.i. is absorbed.
BW	62 kg	Body weight. This is the default value recommended by the WHO GRAM.
EF	365 d/yr	Exposure frequency. The calculated exposure is assumed to occur daily.
ED	1 yr	Exposure duration. The chronic risk of exposure is considered over a one-year period.
AT	365 d	Averaging time. The value is set to compute ADD over a 1-yr period.

Plugging the permethrin values into the equation for ADD yields:

$$SysDose_{inhal,permethrin} = \left[\frac{VP \times MW \times CF_{\frac{mg}{g}}}{R \times T \times AER}\right] \times \left[BR_{sleep} \times T_{sleep}\right] \times \left[\frac{ABS_{resp}}{BW}\right] \times \left[\frac{EF \times ED}{AT}\right]$$

$$SysDose_{inhal,permethrin} = \left[\frac{6.90 \cdot 10^{-6}\ Pa \times 391.3\ \frac{g}{mol} \times 1000\ \frac{mg}{g}}{8.314\ \frac{Pa \cdot m^3}{K \cdot mol} \times 298\ K \times 24}\right] \times \left[0.4\ \frac{m^3}{hr} \times 9\ \frac{hr}{d}\right] \times \left[\frac{1}{62\ kg}\right] \times \left[\frac{365\ \frac{d}{yr} \times 1\ yr}{365\ d}\right]$$

$$SysDose_{inhal,permethrin} = \left[4.5 \cdot 10^{-5}\ \frac{mg}{m^3}\right] \times \left[3.6\ \frac{m^3}{d}\right] \times \left[0.016\ \frac{1}{kg}\right] \times [1]$$

$$SysDose_{inhal,permethrin} = 2.6 \cdot 10^{-6}\ \frac{mg\ a.i.}{kg \cdot d}$$

For pyriproxyfen, the same equation yields:

$$SysDose_{inhal,pyriproxyfen} = 4.1 \cdot 10^{-6} \frac{mg\ a.i.}{kg \cdot d}$$

Chronic Hazard Quotients

The HQ for each exposure scenario is computed by dividing ADD by the appropriate RfD from Annex D. The total HQ for each a.i. in the product is the sum of the HQs for the dermal and inhalation exposure scenarios.

$$HQ_{dermal,permethrin} = \frac{0.032 \frac{mg\ a.i.}{kg \cdot d}}{5.0 \frac{mg\ a.i.}{kg \cdot d}} = 0.0063$$

$$HQ_{inhal,permethrin} = \frac{2.6 \cdot 10^{-6} \frac{mg\ a.i.}{kg \cdot d}}{0.11 \frac{mg\ a.i.}{kg \cdot d}} = 2.3 \cdot 10^{-5}$$

$$HQ_{total,permethrin} = HQ_{dermal,permethrin} + HQ_{inhal,permethrin} = 0.0063 + 2.3 \cdot 10^{-5} = 0.0063$$

$$HQ_{dermal,pyriproxyfen} = \frac{0.016 \frac{mg\ a.i.}{kg \cdot d}}{0.35 \frac{mg\ a.i.}{kg \cdot d}} = 0.045$$

$$HQ_{inhal,pyriproxyfen} = \frac{4.1 \cdot 10^{-6} \frac{mg\ a.i.}{kg \cdot d}}{0.35 \frac{mg\ a.i.}{kg \cdot d}} = 1.2 \cdot 10^{-5}$$

$$HQ_{total,pyriproxyfen} = HQ_{dermal,pyriproxyfen} + HQ_{inhal,pyriproxyfen} = 0.045 + 1.2 \cdot 10^{-5} = 0.045$$

Finally, the total HQ for the receptor is the sum across both a.i. in the product:

$$HQ_{total} = HQ_{total,permethrin} + HQ_{total,pyriproxyfen} = 0.0063 + 0.045 = \mathbf{0.051}$$

Example G3: Chronic Hazard Quotient, Larvicide, Mixing/Loading and Spraying, Worker (Scenarios W-Larv-1–4)

There are two larvicide exposure scenarios for the Worker receptor: dermal exposure to a.i. during mixing/loading of the larvicide product, and dermal exposure to prepared product during spray application. In addition, alternate scenarios are considered for workers following guidelines or lax practices, i.e. with or without personal protective equipment (PPE). Here, risk calculations for these scenarios are illustrated for the larvicide chlorpyrifos .

First, average daily dose (ADD) is calculated for each exposure scenario. The following sections walk through the calculations, using equations and data inputs from Annexes G-2 and G-3, respectively.

Average Daily Dose

All of the exposure calculations for these scenarios take the same form, and differ only in the values for unit exposure (mixing/loading vs. spraying scenarios) and PPE protection factor. Parameters include:

Parameter	Value	Explanation
$TC_{water\ area}$	2.5 mg/m^2	Target areal concentration of a.i. applied to the water surface, obtained from product information.
UE	0.49 mg/kg (mixing/loading) 18.21 mg/kg (spraying)	Unit exposure during mixing/loading. Empirically derived estimates of the mass of a.i. actually contacted per unit mass handled, depending on product formulation and activity (EPA SOP 2012). Values used here are for chlorpyrifos' emulsifiable concentrate formulation (mixing/loading) and backpack sprayer application (spraying).
$CF_{kg/mg}$	1e-6 kg/mg	Conversion factor.
$SR_{water\ area}$	390 m^2/d	Water surface area treated per day. Assumed equal to estimated area sprayed during a single day of IRS spraying (39 m^2/house × 11 houses/d).
ABS_{dermal}	0.1 [*unitless*]	Dermal absorption factor. This is the default value recommended by the WHO GRAM.
PF	0.03 (mixing/loading, with PPE) 0.023 (spraying, with PPE) 1.0 (all scenarios, no PPE) [*unitless*]	Protection factor from PPE [unitless]
BW	62 kg	Body weight. This is the default value recommended by the WHO GRAM.

Parameter	Value	Explanation
EF	156 d/yr	Exposure frequency. Follows WHO GRAM recommendation, which assumes as 6-day work week and 6-month larviciding season.
ED	1 yr	Exposure duration. The chronic risk of exposure is considered over a one-year period.
AT	365 d	Averaging time. The value is set to compute ADD over a 1-yr period.

Plugging values into the ADD equation for the guideline ("With PPE") mixing/loading scenario yields:

$$SysDose_{mix/load,\ PPE} = \left[TC_{\ water\ area} \times UE \times CF_{kg/mg}\right] \times \left[SR_{water\ area}\right] \times \left[\frac{ABS_{dermal} \times PF}{BW}\right] \times \left[\frac{EF \times ED}{AT}\right]$$

$$SysDose_{mix/load,\ PPE} = \left[2.5\,\frac{mg\ a.i.}{m^2} \times 0.49\,\frac{mg}{kg} \times 10^{-6}\,\frac{kg}{mg}\right] \times \left[390\,\frac{m^2}{d}\right] \times \left[\frac{0.1 \times 0.03}{62\ kg}\right] \times \left[\frac{156\,\frac{d}{yr} \times 1\ yr}{365\ d}\right]$$

$$SysDose_{mix/load,\ PPE} = \left[1.2 \cdot 10^{-6}\,\frac{mg\ a.i.}{m^2}\right] \times \left[390\,\frac{m^2}{d}\right] \times \left[0.000048\,\frac{1}{kg}\right] \times [0.43]$$

$$SysDose_{mix/load,PPE} = 9.9 \cdot 10^{-9}\ \frac{mg\ a.i.}{kg \cdot d}$$

For the other scenarios, the same equation yields:

$$SysDose_{mix/load,No\ PPE} = 3.3 \cdot 10^{-7}\,\frac{mg\ a.i.}{kg \cdot d}$$

$$SysDose_{spray,PPE} = 2.8 \cdot 10^{-7}\,\frac{mg\ a.i.}{kg \cdot d}$$

$$SysDose_{spray,No\ PPE} = 1.2 \cdot 10^{-5}\,\frac{mg\ a.i.}{kg \cdot d}$$

Chronic Hazard Quotients

The HQ for each exposure scenario is computed by dividing ADD by the appropriate RfD from Annex D. The total HQ for a larvicide worker is the sum of the HQs for the mixing/loading and spraying scenarios.

$$HQ_{mix/load,PPE} = \frac{9.9 \cdot 10^{-9} \frac{mg\ a.i.}{kg \cdot d}}{0.036 \frac{mg\ a.i.}{kg \cdot d}} = 2.7 \cdot 10^{-7}$$

$$HQ_{spray,PPE} = \frac{2.8 \cdot 10^{-7} \frac{mg\ a.i.}{kg \cdot d}}{0.036 \frac{mg\ a.i.}{kg \cdot d}} = 7.9 \cdot 10^{-6}$$

$$HQ_{total,PPE} = HQ_{mix/load,PPE} + HQ_{spray,PPE} = 2.7 \cdot 10^{-7} + 7.9 \cdot 10^{-6} = 8.2 \cdot 10^{-6}$$

$$HQ_{mix/load,No\ PPE} = \frac{3.3 \cdot 10^{-7} \frac{mg\ a.i.}{kg \cdot d}}{0.036 \frac{mg\ a.i.}{kg \cdot d}} = 9.1 \cdot 10^{-6}$$

$$HQ_{spray,No\ PPE} = \frac{1.2 \cdot 10^{-5} \frac{mg\ a.i.}{kg \cdot d}}{0.036 \frac{mg\ a.i.}{kg \cdot d}} = 0.00034$$

$$HQ_{total,No\ PPE} = HQ_{mix/load,No\ PPE} + HQ_{spray,No\ PPE} = 9.1 \cdot 10^{-6} + 0.00034 = \mathbf{0.00035}$$

Example G4: Chronic Hazard Quotient, Larvicide, Ground Water Contact, Child (Scenario R-Larv-2, 5)

There are two larvicide exposure scenarios via ground water contact for the Child receptor: oral exposure via ingestion of groundwater, and dermal exposure during bathing. Here, risk calculations for these scenarios are illustrated for the larvicide pyriproxyfen.

First, average daily dose (ADD) is calculated for each exposure scenario. The following sections walk through the calculations, using equations and data inputs from Annexes G-2 and G-3, respectively.

Average Daily Dose – Ingestion

Parameters for this calculation include:

Parameter	Value	Explanation
$TC_{water\ area}$	5 mg/m^2	Target areal concentration of a.i. applied to the water surface, obtained from product information.
SG	0.0014	Concentration factor calculated from the SCI-GROW model, based on a.i. K_{oc} and half-life in the soil. Calculations for this value are not shown.
WIR	1 L	Water ingestion rate. Follows WHO GRAM recommendations, which vary by receptor. This is the default value for a child.
$CF_{m3/L}$	0.001 m^3/L	Conversion factor
ABS_{oral}	1 [*unitless*]	Oral absorption factor. This is the default value recommended by the WHO GRAM, which conservatively assumes that 100% of ingested a.i. is absorbed.
BW	32 kg	Body weight. This is the default value recommended by the WHO GRAM.
EF	365 d/yr	Exposure frequency. The calculated exposure is assumed to occur daily.
ED	1 yr	Exposure duration. The chronic risk of exposure is considered over a one-year period.

Parameter	Value	Explanation
AT	365 d	Averaging time. The value is set to compute ADD over a 1-yr period.

Plugging these values into the ADD equation yields:

$$SysDose_{ingestion} = [TC_{\ water\ area} \times SG] \times \left[WIR \times CF_{m3/L}\right] \times \left[\frac{ABS_{oral}}{BW}\right] \times \left[\frac{EF \times ED}{AT}\right]$$

$$SysDose_{ingestion} = \left[5\,\frac{mg\ a.i.}{m^2} \times 0.0014\right] \times \left[1\,\frac{L}{d} \times 0.001\,\frac{m^3}{L}\right] \times \left[\frac{1}{32\ kg}\right] \times \left[\frac{365\,\frac{d}{yr} \times 1\ yr}{365\ d}\right]$$

$$SysDose_{ingestion} = \left[0.0070\,\frac{mg\ a.i.}{m^3}\right] \times \left[0.001\,\frac{m^3}{d}\right] \times \left[0.031\,\frac{1}{kg}\right] \times [1]$$

$$SysDose_{ingestion} = 2.2 \cdot 10^{-7}\,\frac{mg\ a.i.}{kg \cdot d}$$

Average Daily Dose – Dermal

Parameters for this calculation include:

Parameter	Value	Explanation
$TC_{water\ area}$	5 mg/m^2	Target areal concentration of a.i. applied to the water surface, obtained from product information.
SG	0.0014	Concentration factor calculated from the SCI-GROW model, based on a.i. K_{OC} and half-life in the soil. Calculations for this value are not shown.
FT	0.0001 m	Film thickness of liquid in contact with immersed body. This is the default value recommended by the WHO GRAM (0.1 mm), converted to meters to match other parameters.

Parameter	Value	Explanation
SA_{body}	1.08 m^2/d	Body surface area contact rate. Assumes one bath per day, during which entire body area contacts contaminated ground water.
ABS_{dermal}	0.1 [*unitless*]	Dermal absorption factor. This is the default value recommended by the WHO GRAM.
BW	32 kg	Body weight. This is the default value recommended by the WHO GRAM.
EF	365 d/yr	Exposure frequency. The calculated exposure is assumed to occur daily.
ED	1 yr	Exposure duration. The chronic risk of exposure is considered over a one-year period.
AT	365 d	Averaging time. The value is set to compute ADD over a 1-yr period.

Plugging these values into the ADD equation yields:

$$SysDose_{dermal} = [TC_{\ water\ area} \times SG] \times [FT \times SA_{body}] \times \left[\frac{ABS_{dermal}}{BW}\right] \times \left[\frac{EF \times ED}{AT}\right]$$

$$SysDose_{dermal} = \left[5\,\frac{mg\ a.i.}{m^2} \times 0.0014\right] \times \left[0.0001\,m \times 1.08\,\frac{m^2}{d}\right] \times \left[\frac{0.1}{32\,kg}\right] \times \left[\frac{365\,\frac{d}{yr} \times 1\,yr}{365\,d}\right]$$

$$SysDose_{dermal} = \left[0.0070\,\frac{mg\ a.i.}{m^3}\right] \times \left[0.000108\,\frac{m^3}{d}\right] \times \left[0.0031\,\frac{1}{kg}\right] \times [1]$$

$$SysDose_{dermal} = 2.4 \cdot 10^{-9}\,\frac{mg\ a.i.}{kg \cdot d}$$

Chronic Hazard Quotients

The hazard quotient (HQ) for each exposure scenario is computed by dividing ADD by the appropriate reference dose (RfD) from Annex D. The total HQ for the receptor is the sum of the HQs for all scenarios.

$$HQ_{ingestion} = \frac{2.2 \cdot 10^{-7} \frac{mg\ a.i.}{kg \cdot d}}{0.35 \frac{mg\ a.i.}{kg \cdot d}} = 6.2 \cdot 10^{-7}$$

$$HQ_{dermal} = \frac{2.4 \cdot 10^{-9} \frac{mg\ a.i.}{kg \cdot d}}{0.35 \frac{mg\ a.i.}{kg \cdot d}} = 6.7 \cdot 10^{-9}$$

$$HQ_{total} = HQ_{ingestion} + HQ_{dermal} = 6.2 \cdot 10^{-7} + 6.7 \cdot 10^{-9} = \mathbf{6.3 \cdot 10^{-7}}$$

ANNEX H – WORKED EXAMPLES OF THE ECOLOGICAL RISK ASSESSMENT PROCESS

The persistence of a pesticide can be measured by how long the pesticide will remain in various environmental compartments. Half-life values of a pesticide in water, soil and sediment can be used to determine if the chemical will be relatively high, moderate or have a low chance of persistence once it is released in to the environment. Similarly, the octanol-water coefficient (K_{ow}) is ratio of the solubility of a chemical in octanol and water, where low K_{ow} values represent that the chemical will be more hydrophilic and present in water. The organic carbon water coefficient (K_{oc}) is a similar measure that will determine if the chemical will preferentially persist in the soil. The data cut off values for high, medium and low half-life and partition coefficients were compiled to determine a relative scale for persistence (Table 1). The associated half-life and partition coefficient data were compiled specifically for spinosad (Table 2). Table 1. Criteria Values for Persistence

TABLE 1. CRITERIA VALUES FOR PERSISTENCE

	Half life in water, soil, and sediment (days)	**K_{ow} - water**	**K_{oc} - soil**
High	>180	>20000	>32000
Medium	>60 - 180	3000-20000	30-32000
Low	<60	<3000	<30
Reference: USEPA, 2012; Kent, 2012			

TABLE 2. SPINOSAD DATA VALUES USED FOR PERSISTENCE CRITERIA

Spinosad	**Value**	**Units**	**Reference**
Half-life soil	8.68	days	Toxnet
Half-life soil	9.44	days	Toxnet
Half-life soil	9	days	AMS, 2002
Half-life soil	17	days	AMS, 2002
K_{oc}	35838	unitless	DPR, 1995
K_{ow}	54.6	unitless	DPR, 1995
K_{ow}	90	unitless	DPR, 1995
Half-life water	>30	days	Toxnet

In this example, there are four data values for the half-life of soil that, when compared to the cut-off values in Table 1, are all considered to be low. However, the K_{oc} value for spinosad is high, implying the possibility for it to persist in soil. Therefore, in the heat map (Table 3.) there is a red cell for low persistence in the soil since

there are 4 or more data values at that level. There is a green cell for medium since there are no data values in that range of persistence, and finally there is one data value to support high persistence in soil, so that cell is yellow. In this example, there are no data values for persistence in the sediment, so all of those cells in the heat map are green. There is one half-life value for spinosad in water and two different K_{ow} values for spinosad. All of these values fall in to the "low persistence" category, therefore the cell is colored orange (2-3 data values). There are no data values that fall in to the medium or high level of persistence in water, which is why those cells are green.

TABLE 3. HEAT MAP FOR AVAILABLE DATA FOR PERSISTENCE OF SPINOSAD

Spinosad	**Environmental Compartment**			
Persistence		Soil	Sediment	Water
	High			
	Medium			
	Low			

The bioaccumulation potential of a pesticide is measured by bioconcentration factors (BCF) and octanol-water partition coefficients (K_{ow}). The BCF is a measure of the extent of chemical sharing between an ecological receptor and the surrounding environment. The criteria cut-off values for high, medium and low were compiled to determine a relative scale for bioaccumulation (Table 4). The associated BCF and partition coefficient data (log K_{ow}) were compiled specifically for spinosad (Table 5).

TABLE 4. CRITERIA VALUES FOR BIOACCUMULATION

	Bioconcentration factor (BCF) - Fish	**Log K_{ow} - terrestrial systems**	**Low K_{ow} - aquatic systems**
High	>5000	>4 - 6	>5 - 6
Medium	>=1000 - 5000	>=2 - 4	4 - 5, >6
Low	<1000	<2; >6	<4
Reference: ECETOC, 2014; USEPA, 2012			

TABLE 5. SPINOSAD DATA VALUES USED FOR BIOACCUMULATION CRITERIA

Spinosad	**Value**	**Units**	**Reference**
Log K_{ow}	4.1	unitless	Toxnet
Log K_{ow}	4.01	unitless	Toxnet
BCF - Fish	33	unitless	Dow Chemical
BCF - Fish	33	unitless	Dow Chemical

In this example, there are two K_{ow} data points for spinosad that are considered low for the potential to bioaccumulate in water. Combine this data with the very low BCF values for fish, and there are 4 data values supporting a low potential to bioaccumulate in fish (red cell). However the same K_{ow} values are considered high for the potential to bioaccumulate in soil, therefore the high cell for terrestrial invertebrates is in orange. The rest of the cells in the heat map are green due to no values associated with those ecological receptor-bioaccumulation levels.

TABLE 6. HEAT MAP FOR AVAILABLE DATA FOR BIOACCUMULATION OF SPINOSAD

Spinosad	**Ecological Receptor Category**			
Bioaccum-ulation		Terr. Invert.	Aquatic Invert.	Fish
	High			
	Medium			
	Low			

The toxicity potential of a pesticide is measured by acute and chronic exposures to various ecological receptors, such as the LD50, which is the amount of an ingested substance that kills 50% of a specific population. Another example is the no observed adverse effect level (NOAEL), which is the level of exposure to an organism where there is no biologically or statistically significant (e.g., alteration of morphology, functional capacity, growth, development or life span) increase in the frequency or severity of any adverse effect in the exposed population. The pesticides are released in to the environment, which can then affect terrestrial and aquatic systems. Therefore is in necessary to determine the potential toxicity to many different ecological receptors from microorganisms, honeybees, fish, birds to terrestrial animals. The high, medium and low cut off values for toxicity for 12 different ecological receptors was compiled (Table 7). The associated toxicity data were compiled specifically for spinosad (Table 8).

TABLE 7. CRITERIA VALUES FOR TOXICITY

	Avian: Oral	**Avian: Dietary**	**Mammals: Oral**	**Mammals: Dermal**	**Terrestrial animals**	**Non-target Insects**
Duration	Acute		Acute	Acute	Chronic	Acute
Test	LD50	LD50	LD50	LD50	NOAEL	LD50
Units	mg/kg	ppm	mg/kg	mg/kg	mg/kg bw	ug/bee
High	<50	<500	<50	<200	<=0.5	<2
Medium	500-50	1000-500	500 - 50	2000 - 200	>0.5 - <=5	2 - 11
Low	>501	>1001	>500	>2000	>5 - <=50	>11
Reference:	USEPA, 2012	USEPA, 2012	USEPA, 2012	WHO, 2009	ILO, 2001	USEPA, 2014

	Microorganisms	Fish	Aquatic Organisms	Aquatic invertebrates	Soil dwelling Invertebrates	Soil dwelling Invertebrates
Duration	Chronic	Chronic	Acute	Chronic	Acute	Chronic
Test	EC50	LC50	LC50	EC50	EC50	NOEC
Units	mg/kg bw	mg/L	mg/L	mg/L	mg/kg soil dw	mg/kg
High	<10	<=1	<1	<=1	<10	<10
Medium	100-10	>1-10	<10 - 1	>1-10	100-10	100-10
Low	>100	>10-100	>10	>10-100	>100	>100
Reference:	Hartmann, 2014	ILO, 2001	USEPA, 2012	ILO, 2001	Hartmann, 2014	Hartmann, 2014

TABLE 8. SPINOSAD DATA VALUES USED FOR TOXICITY CRITERIA

Spinosad	**Value**	**Units**	**Reference**	**Eco Receptor**
LD50 Rat Oral	3738	mg/kg	Toxnet	Terr. Vert.
LD50 Rabbit Dermal	>2000	mg/kg	Toxnet	Terr. Vert.
LD50 Mallard duck Oral	>1333	mg/kg	Toxnet	Terr. Vert.
LD50 Mallard duck	5253	mg/kg	Thompson, 2000	Terr. Vert.
LD50 Bobwhite quail	>1333	mg/kg	Toxnet	Terr. Vert.
NOAEL Rat	8.2	mg/kg/day	HSDB, 2009	Terr. Vert.
NOAEL Mouse	7.5	mg/kg/day	HSDB, 2009	Terr. Vert.
NOAEL Mouse	11.4	mg/kg/day	HSDB, 2009	Terr. Vert.
NOAEL Rabbit	1000	mg/kg/day	HSDB, 2009	Terr. Vert.
NOAEL Dog	4.9	mg/kg/day	HSDB, 2009	Terr. Vert.
NOAEL Dog	2.7	mg/kg/day	HSDB, 2009	Terr. Vert.
NOAEL Rat	2.4	mg/kg/day	HSDB, 2009	Terr. Vert.
LD50 Honey bee	0.0029	ug/bee	Toxnet	Terr. Invert.
LC50 Rainbow trout	30	ppm	Toxnet	Fish
LC50 Carp	5	ppm	DPR, 1995	Fish
LC50 Bluegill sunfish	5.94	ppm	Toxnet	Fish
LC50 Sheepshead minnow	7.87	ppm	Toxnet	Fish
LC50 Daphnia	7.9	ppm	Dow, 2001	Aquatic Invert.
LC50 Grass shrimp	>9.76	ppm	Toxnet	Aquatic Invert.

TABLE 8. SPINOSAD DATA VALUES USED FOR TOXICITY CRITERIA

Spinosad	**Value**	**Units**	**Reference**	**Eco Receptor**
EC50 Eastern oyster	0.295	ppm	Dow, 2001	Aquatic Invert.
EC50 Green algae	>105.5	ppm	DPR, 1995	Microalgae
EC50 Freshwater diatom	0.107	ppm	DPR, 1995	Microalgae
EC50 Duckweed	10.6	ppm	DPR, 1995	Microalgae

There are 12 data points for toxicity of spinosad in terrestrial vertebrates. Nine of these values are considered low according to the criteria in Table 8, therefore the cell for low is in red. There are 3 toxicity values for terrestrial animals that are medium, so that cell is outlined in orange. There are no data points implying that spinosad is highly toxic to terrestrial animals, so that cell is green. There is only one data point for terrestrial invertebrates (e.g., honeybee) and spinosad is highly toxic to bees and that cell is yellow. There are no associated data points for the rest of terrestrial invertebrates or soil microbiota toxicity levels.

TABLE 9. HEAT MAP FOR AVAILABLE DATA FOR TOXICITY OF SPINOSAD IN THE TERRESTRIAL SYSTEM

Spinosad	**Ecological Receptor Category**			
		Soil microbiota	Terr. Invert.	Terr. Vert.
Toxicity	High			
	Medium			
	Low			

There are a total of 10 data values for the toxicity of spinosad to aquatic system receptors. There are 3 medium and 1 low toxicity values for fish (orange and yellow cells, respectively). There is one high toxicity value for aquatic invertebrates, and two medium toxicity values (yellow and orange cells). Finally, there is one data point for high, one for medium, and one for low toxicity for spinosad to microalgae, so all three cells are yellow.

TABLE 10. HEAT MAP FOR AVAILABLE DATA FOR TOXICITY OF SPINOSAD IN THE AQUATIC SYSTEM

Spinosad	**Ecological Receptor Category**			
		Microalgae	Aq. Invert.	Fish
Toxicity	High			
	Medium			
	Low			

USAID
FROM THE AMERICAN PEOPLE

ANNEX I

ENVIRONMENTAL COMPLIANCE PROCEDURES

TITLE 22, CODE OF FEDERAL REGULATIONS, PART 216

Photo Caption: Wildlife Conservation Society (WCS) field technician Dorian McCoy releasing a hawksbill sea turtle in the Pearl Cays, Nicaragua. Protection of this endangered sea turtle is one of the goals of WCS Nicaragua Marine Program operating in the Pearl Lagoon basin on the Atlantic coast of Nicaragua.

Foreword

This brochure provides a handy copy of the environmental impact assessment procedures used by the U.S. Agency for International Development (USAID). They have been promulgated as Title 22 of the Code of Federal Regulations, Part 216 (22 CFR 216).

The procedures are used on every program, project, activity and amendment USAID funds to ensure the wise use of American taxpayer money through thoughtful, environmentally sound economic development. In the thirty years in which USAID has been applying these procedures and their predecessors, we have learned that they are most successful when everyone involved in a USAID-funded effort accepts responsibility for understanding and implementing them. Through this process, together we:

- **Create modern, state-of-the-art development**
- **Achieve optimal economic results with every dollar invested**
- **Avoid harming people in both our partner countries and the U.S.**
- **Avert unintended negative economic growth**
- **Reinforce practical civil society and democracy through transparency and public participation**
- **Reduce diplomatic incidents**
- **Engender public trust and confidence in USAID**
- **Comply with the law**

Additional guidance on applying 22 CFR 216 is found in USAID's Automated Directives System, Chapter 204. This is available on the internet at:
http://www.usaid.gov/policy/ads/200/204.pdf

An electronic copy of 22 CFR 216, along with many helpful guidelines, training books, sample documents and contacts of USAID professionals who can assist can be found on the internet at:
http://www.usaid.gov/our_work/environment/compliance/index.html

James Hester
Agency Environmental Coordinator
U.S. Agency for International Development

United States Agency for International Development
Title 22, Code of Federal Regulation, Part 216
Agency Environmental Procedures

Preface

These procedures have been revised based on experience with previous ones agreed to in settlement of a lawsuit brought against the Agency in 1975. The Procedures are Federal Regulations and therefore, it is imperative that they be followed in the development of Agency programs.

In preparing these Regulations, some interpretations and definitions have been drawn from Executive Order No. 12114 of January 1979, on the application of the National Environmental Policy Act (NEPA) to extraterritorial situations. Some elements of the revised regulations on NEPA issued by the President's Council on Environmental Quality have also been adopted. Examples are: The definition of significant impact, the concept of scoping of issues to be examined in a formal analysis, and the elimination of certain A.I.D. activities from the requirement for environmental review.

In addition, these procedures: 1) provide advance notice that certain types of projects will automatically require detailed environmental analysis thus eliminating one step in the former process and permitting early planning for this activity; 2) permit the use of specially prepared project design considerations or guidance to be substituted for environmental analysis in selected situations; 3) advocate the use of indigenous specialists to examine pre-defined issues during the project design stage; 4) clarify the role of the Bureau's Environmental Officer in the review and approval process, and 5) permit in certain circumstances, projects to go forward prior to completion of environmental analysis.

Note that only minimal clarification changes have been made in those sections dealing with the evaluation and selection of pesticides to be supported by A.I.D. in projects or of a non-project.

INTERNATIONAL DEVELOPMENT COOPERATION AGENCY

U.S. Agency for International Development

22 CFR PART 216

ENVIRONMENTAL PROCEDURES

Authority: 42 U.S.C. 4332; 22 U.S.C. 2381.

Source: 41 FR 26913, June 30, 1976.

§216.1 Introduction.

(a) Purpose. In accordance with sections 118(b) [now section 117(c)] and 621 of the Foreign Assistance Act of 1961, as amended, (the FAA) the following general procedures shall be used by A.I.D. to ensure that environmental factors and values are integrated into the A.I.D. decision-making process. These procedures also assign responsibility within the Agency for assessing the environmental effects of A.I.D.'s actions. These procedures are consistent with Executive Order 12114, issued January 4, 1979, entitled Environmental Effects Abroad of Major Federal Actions, and the purposes of the National Environmental Policy Act of 1970, as amended (42 U.S.C. 4371 et seq.)(NEPA). They are intended to implement the requirements of NEPA as they affect the A.I.D. program.

(b) Environmental Policy. In the conduct of its mandate to help upgrade the quality of life of the poor in developing countries, A.I.D. conducts a broad range of activities. These activities address such basic problems as hunger, malnutrition, overpopulation, disease, disaster, deterioration of the environment and the natural resource base, illiteracy as well as the lack of adequate housing and transportation. Pursuant to the FAA, A.I.D. provides development assistance in the form of technical advisory services, research, training, construction and commodity support. In addition, A.I.D. conducts programs under the Agricultural Trade Development and Assistance Act of 1954 (Pub. L. 480) that are designed to combat hunger, malnutrition and to facilitate economic development. Assistance programs are carried out under the foreign policy guidance of the Secretary of State and in cooperation with the governments of sovereign states. Within this framework, it is A.I.D. policy to:

(1) Ensure that the environmental consequences of A.I.D.-financed activities are identified and considered by A.I.D. and the host country prior to a final decision to proceed and that appropriate environmental safeguards are adopted;

(2) Assist developing countries to strengthen their capabilities to appreciate and effectively evaluate the potential environmental effects of proposed development strategies and projects, and to select, implement and manage effective environmental programs;

(3) Identify impacts resulting from A.I.D.'s actions upon the environment, including those aspects of the biosphere which are the common and cultural heritage of all mankind; and

(4) Define environmental limiting factors that constrain development and identify and carry out activities that assist in restoring the renewable resource base on which sustained development depends.

(c) Definitions.

(1) CEQ Regulations. Regulations promulgated by the President's Council on Environmental Quality (CEQ) (Federal Register, Volume 43, Number 230, November 29, 1978) under the authority of NEPA and Executive Order 11514, entitled Protection and Enhancement of Environmental Quality (March 5, 1970) as amended by Executive Order 11991 (May 24, 1977).

(2) Initial Environmental Examination. An Initial Environmental Examination is the first review of the reasonably foreseeable effects of a proposed action on the environment. Its function is to provide a brief statement of the factual basis for a Threshold Decision as to whether an Environmental Assessment or an Environmental Impact Statement will be required.

(3) Threshold Decision. A formal Agency decision which determines, based on an Initial Environmental Examination, whether a proposed Agency action is a major action significantly affecting the environment.

(4) Environmental Assessment. A detailed study of the reasonably foreseeable significant effects, both beneficial and adverse, of a proposed action on the environment of a foreign country or countries.

(5) Environmental Impact Statement. A detailed study of the reasonably foreseeable environmental impacts, both positive and negative, of a proposed A.I.D. action and its reasonable alternatives on the United States, the global environment or areas outside the jurisdiction of any nation as described in §216.7 of these procedures. It is a specific document having a definite format and content, as provided in NEPA and the CEQ Regulations. The required form and content of an Environmental Impact Statement is further described in §216.7 infra.

(6) Project Identification Document (PID). An internal A.I.D. document which initially identifies and describes a proposed project.

(7) Program Assistance Initial Proposal (PAIP). An internal A.I.D. document used to initiate and identify proposed nonproject assistance, including commodity import programs. It is analogous to the PID.

(8) Project Paper (PP). An internal A.I.D. document which provides a definitive description and appraisal of the project and particularly the plan or implementation.

(9) Program Assistance Approval Document (PAAD). An internal A.I.D. document approving nonproject assistance. It is analogous to the PP.

(10) Environment. The term environment, as used in these procedures with respect to effects occurring outside the United States, means the natural and physical environment. With respect to effects occurring within the United States see §216.7(b).

(11) Significant Effect. With respect to effects on the environment outside the United States, a proposed action has a significant effect on the environment if it does significant harm to the environment.

(12) Minor Donor. For purposes of these procedures, A.I.D. is a minor donor to a multidonor project when A.I.D. does not control the planning or design of the multidonor project and either:

(i) A.I.D.'s total contribution to the project is both less than $1,000,000 and less than 25 percent of the estimated project cost, or

(ii) A.I.D.'s total contribution is more than $1,000,000 but less than 25 percent of the estimated project cost and the environmental procedures of the donor in control of the planning of design of the project are followed, but only if the A.I.D. Environmental Coordinator determines that such procedures are adequate.

§216.2 Applicability of procedures.

(a) Scope. Except as provided in §216.2(b), these procedures apply to all new projects, programs or activities authorized or approved by A.I.D. and to substantive amendments or extensions of ongoing projects, programs, or activities.

(b) Exemptions.

(1) Projects, programs or activities involving the following are exempt from these procedures:

(i) International disaster assistance;

(ii) Other emergency circumstances; and

(iii) Circumstances involving exceptional foreign policy sensitivities.

(2) A formal written determination, including a statement of the justification therefore, is required for each project, program or activity for which an exemption is made under paragraphs (b)(l) (ii) and (iii) of this section, but is not required for projects, programs or activities under paragraph (b)(l)(i) of this section. The determination shall be made either by the Assistant Administrator having responsibility for the program, project or activity, or by the Administrator,

where authority to approve financing has been reserved by the Administrator. The determination shall be made after consultation with CEQ regarding the environmental consequences of the proposed program, project or activity.

(c) Categorical Exclusions.

(1) The following criteria have been applied in determining the classes of actions included in §216.2(c)(2) for which and Initial Environmental Examination, Environmental Assessment and Environmental Impact Statement generally are not required:

(i) The action does not have an effect on the natural or physical environment;

(ii) A.I.D. does not have knowledge of or control over, and the objective of A.I.D. in furnishing assistance does not require, either prior to approval of financing or prior to implementation of specific activities, knowledge of or control over, the details of the specific activities that have an effect on the physical and natural environment for which financing is provided by A.I.D.;

(iii) Research activities which may have an affect on the physical and natural environment but will not have a significant effect as a result of limited scope, carefully controlled nature and effective monitoring.

(2) The following classes of actions are not subject to the procedures set forth in §216.3, except to the extent provided herein;

(i) Education, technical assistance, or training programs except to the extent such programs include activities directly affecting the environment (such as construction of facilities, etc.);

(ii) Controlled experimentation exclusively for the purpose of research and field evaluation which are confined to small areas and carefully monitored;

(iii)Analyses, studies, academic or research workshops and meetings;

(iv) Projects in which A.I.D. is a minor donor to a multidonor project and there is no potential significant effects upon the environment of the United States, areas outside any nation's jurisdiction or endangered or threatened species or their critical habitat;

(v) Document and information transfers;

(vi) Contributions to international, regional or national organizations by the United States which are not for the purpose of carrying out a specifically identifiable project or projects;

(vii) Institution building grants to research and educational institutions in the United States such as those provided for under section 122(d) and Title XII of Chapter 2 of Part I of the FAA (22 USCA §§2151 p. (b) 2220a. (1979));

(viii) Programs involving nutrition, health care or population and family planning services except to the extent designed to include activities directly affecting the environment (such as construction of facilities, water supply systems, waste water treatment, etc.)

(ix) Assistance provided under a Commodity Import Program when, prior to approval, A.I.D. does not have knowledge of the specific commodities to be financed and when the objective in furnishing such assistance requires neither knowledge, at the time the assistance is authorized, nor control, during implementation, of the commodities or their use in the host country.

(x) Support for intermediate credit institutions when the objective is to assist in the capitalization of the institution or part thereof and when such support does not involve reservation of the right to review and approve individual loans made by the institution;

(xi) Programs of maternal or child feeding conducted under Title II of Pub. L. 480;

(xii) Food for development programs conducted by food recipient countries under Title III of Pub. L. 480, when achieving A.I.D.'s objectives in such programs does not require knowledge of or control over the details of the specific activities conducted by the foreign country under such program;

(xiii) Matching, general support and institutional support grants provided to private voluntary organizations (PVOs) to assist in financing programs where A.I.D.'s objective in providing such financing does not require knowledge of or control over the details of the specific activities conducted by the PVO;

(xiv) Studies, projects or programs intended to develop the capability of recipient countries to engage in development planning, except to the extent designed to result in activities directly affecting the environment (such as construction of facilities, etc.); and

(xv) Activities which involve the application of design criteria or standards developed and approved by A.I.D.

(3) The originator of a project, program or activity shall determine the extent to which it is within the classes of actions described in paragraph (c)(2) of this section. This determination shall be made in writing and be submitted with the PID, PAIP or comparable document. This determination, which must include a brief statement supporting application of the exclusion shall be reviewed by the Bureau Environmental Officer in the same manner as a Threshold Decision under §216.3(a)(2) of these procedures. Notwithstanding paragraph (c)(2) of this section, the procedures set forth in §216.3 shall apply to any project, program or activity included in the classes of actions listed in paragraph (c)(2) of this section, or any aspect or component thereof, if at any time in the design, review or approval of the activity it is determined that the project, program or activity, or

aspect or component thereof, is subject to the control of A.I.D. and may have a significant effect on the environment.

(d) Classes of Actions Normally Having a Significant Effect on the Environment.

(1) The following classes of actions have been determined generally to have a significant effect on the environment and an Environmental Assessment or Environmental Impact Statement, as appropriate, will be required:

(i) Programs of river basin development;

(ii) Irrigation or water management projects, including dams and impoundments;

(iii) Agricultural land leveling;

(iv) Drainage projects;

(v) Large scale agricultural mechanization;

(vi) New lands development;

(vii) Resettlement projects;

(viii) Penetration road building or road improvement projects;

(ix) Powerplants;

(x) Industrial plants;

(xi) Potable water and sewerage projects other than those that are smallscale.

(2) An Initial Environmental Examination normally will not be necessary for activities within the classes described in §216.2(d), except when the originator of the project believes that the project will not have a significant effect on the environment. In such cases, the activity may be subjected to the procedures set forth in §216.3.

(e) Pesticides. The exemptions of §216.2(b)(l) and the categorical exclusions of §216.2(c)(2) are not applicable to assistance for the procurement or use of pesticides.

§216.3 Procedures.

(a) General Procedures.

(1) Preparation of the Initial Environmental Examination. Except as otherwise provided, an Initial Environmental Examination is not required for activities identified in §216.2(b)(1), (c)(2), and (d). For all other A.I.D. activities described in §216.2(a) an Initial Environmental Examination will be prepared by

the originator of an action. Except as indicated in this section, it should be prepared with the PID or PAIP. For projects including the procurement or use of pesticides, the procedures set forth in §216.3(b) will be followed, in addition to the procedures in this paragraph. Activities which cannot be identified in sufficient detail to permit the completion of an Initial Environmental Examination with the PID or PAIP, shall be described by including with the PID or PAIP:

(i) An explanation indicating why the Initial Environmental Examination cannot be completed;

(ii) an estimate of the amount of time required to complete the Initial Environmental Examination; and

(iii) a recommendation that a Threshold Decision be deferred until the Initial Environmental Examination is completed. The responsible Assistant Administrator will act on the request for deferral concurrently with action on the PID or PAIP and will designate a time for completion of the Initial Environmental Examination. In all instances, except as provided in §216.3(a)(7), this completion date will be in sufficient time to allow for the completion of an Environmental Assessment or Environmental Impact Statement, if required, before a final decision is made to provide A.I.D. funding for the action.

(2) Threshold Decision.

(i) The Initial Environmental Examination will include a Threshold Decision made by the officer in the originating office who signs the PID or PAIP. If the Initial Environmental Examination is completed prior to or at the same time as the PID or PAIP, the Threshold Decision will be reviewed by the Bureau Environmental Officer concurrently with approval of the PID or PAIP. The Bureau Environmental Officer will either concur in the Threshold Decision or request reconsideration by the officer who made the Threshold Decision, stating the reasons for the request. Differences of opinion between these officers shall be submitted for resolution to the Assistant Administrator at the same time that the PID is submitted for approval.

(ii) An Initial Environmental Examination, completed subsequent to approval of the PID or PAIP, will be forwarded immediately together with the Threshold Determination to the Bureau Environmental Officer for action as described in this section.

(iii) A Positive Threshold Decision shall result from a finding that the proposed action will have a significant effect on the environment. An Environmental Impact Statement shall be prepared if required pursuant to §216.7. If an impact statement is not required, an Environmental Assessment will be prepared in accordance with §216.6. The cognizant Bureau or Office will record a Negative Determination if the proposed action will not have a significant effect on the environment.

(3) Negative Declaration. The Assistant Administrator, or the Administrator in actions for which the approval of the Administrator is required for the authorization of financing, may make a Negative Declaration, in writing, that the Agency will not develop an Environmental Assessment or an Environmental Impact Statement regarding an action found to have a significant effect on the environment when:

(i) a substantial number of Environmental Assessments or Environmental Impact Statements relating to similar activities have been prepared in the past, if relevant to the proposed action,

(ii) the Agency has previously prepared a programmatic Statement or Assessment covering the activity in question which has been considered in the development of such activity, or

(iii) the Agency has developed design criteria for such an action which, if applied in the design of the action, will avoid a significant effect on the environment.

(4) Scope of Environmental Assessment or Impact Statement.

(i) Procedure and Content. After a Positive Threshold Decision has been made, or a determination is made under the pesticide procedures set forth in §216.3(b) that an Environmental Assessment or Environmental Impact Statement is required, the originator of the action shall commence the process of identifying the significant issues relating to the proposed action and of determining the scope of the issues to be addressed in the Environmental Assessment or Environmental Impact Statement. The originator of an action within the classes of actions described in §216.2(d) shall commence this scoping process as soon as practicable. Persons having expertise relevant to the environmental aspects of the proposed action shall also participate in this scoping process. (Participants may include but are not limited to representatives of host governments, public and private institutions, the A.I.D. Mission staff and contractors.) This process shall result in a written statement which shall include the following matters:

(a) A determination of the scope and significance of issues to be analyzed in the Environmental Assessment or Impact Statement, including direct and indirect effects of the project on the environment.

(b) Identification and elimination from detailed study of the issues that are not significant or have been covered by earlier environmental review, or approved design considerations, narrowing the discussion of these issues to a brief presentation of why they will not have a significant effect on the environment.

(c) A description of:

(1) the timing of the preparation of environmental analyses, including phasing if appropriate,

(2) variations required in the format of the Environmental Assessment, and

(3) the tentative planning and decision-making schedule; and

(d) A description of how the analysis will be conducted and the disciplines that will participate in the analysis.

(ii) These written statements shall be reviewed and approved by the Bureau Environmental Officer.

(iii) Circulation of Scoping Statement. To assist in the preparation of an Environmental Assessment, the Bureau Environmental Officer may circulate copies of the written statement, together with a request for written comments, within thirty days, to selected federal agencies if that Officer believes comments by such federal agencies will be useful in the preparation of an Environmental Assessment. Comments received from reviewing federal agencies will be considered in the preparation of the Environmental Assessment and in the formulation of the design and implementation of the project, and will, together with the scoping statement, be included in the project file.

(iv) Change in Threshold Decision. If it becomes evident that the action will not have a significant effect on the environment (i.e., will not cause significant harm to the environment), the Positive Threshold Decision may be withdrawn with the concurrence of the Bureau Environmental Officer. In the case of an action included in §216.2(d)(2), the request for withdrawal shall be made to the Bureau Environmental Officer.

(5) Preparation of Environmental Assessments and Environmental Impact Statement. If the PID or PAIP is approved, and the Threshold Decision is positive, or the action is included in §216.2(d), the originator of the action will be responsible for the preparation of an Environmental Assessment or Environmental Impact Statement as required. Draft Environmental Impact Statements will be circulated for review and comment as part of the review of Project Papers and as outlined further in §216.7 of those procedures. Except as provided in §216.3(a)(7), final approval of the PP or PAAD and the method of implementation will include consideration of the Environmental Assessment or final Environmental Impact Statement.

(6) Processing and Review Within A.I.D.

(i) Initial Environmental Examinations, Environmental Assessments, and final Environmental Impact Statements will be processed pursuant to standard A.I.D. procedures for project approval documents. Except as provided in §216.3(a)(7), Environmental Assessments and final Environmental Impact Statements will be reviewed as an integral part of the Project Paper or equivalent document. In addition to these procedures, Environmental Assessments will be reviewed and cleared by the Bureau Environmental Officer. They may also be reviewed by the

Agency's Environmental Coordinator who will monitor the Environmental Assessment process.

(ii) When project approval authority is delegated to field posts, Environmental Assessments shall be reviewed and cleared by the Bureau Environmental Officer prior to the approval of such actions.

(iii) Draft and final Environmental Impact Statements will be reviewed and cleared by the Environmental Coordinator and the Office of the General Counsel.

(7) Environmental Review After Authorization of Financing.

(i) Environmental review may be performed after authorization of a project, program or activity only with respect to subprojects or significant aspects of the project, program or activity that are unidentified at the time of authorization. Environmental review shall be completed prior to authorization for all subprojects and aspects of a project, program or activity that are identified.

(ii) Environmental review should occur at the earliest time in design or implementation at which a meaningful review can be undertaken, but in no event later than when previously unidentified subprojects or aspects of projects, programs or activities are identified and planned. To the extent possible, adequate information to undertake deferred environmental review should be obtained before funds are obligated for unidentified subprojects or aspects of projects, programs or activities. (Funds may be obligated for the other aspects for which environmental review has been completed.) To avoid an irreversible commitment of resources prior to the conclusion of environmental review, the obligation of funds can be made incrementally as subprojects or aspects of projects, programs or activities are identified; or if necessary while planning continues, including environmental review, the agreement or other document obligating funds may contain appropriate covenants or conditions precedent to disbursement for unidentified subprojects or aspects of projects, programs or activities.

(iii) When environmental review must be deferred beyond the time some of the funds are to be disbursed (e.g., long lead times for the delivery of goods or services), the project agreement or other document obligating funds shall contain a covenant or covenants requiring environmental review, including an Environmental Assessment or Environmental Impact Statement, when appropriate, to be completed and taken into account prior to implementation of those subprojects or aspects of the project, program or activity for which environmental review is deferred. Such covenants shall ensure that implementation plans will be modified in accordance with environmental review if the parties decide that modifications are necessary.

(iv) When environmental review will not be completed for an entire project, program or activity prior to authorization, the Initial Environmental Examination and

Threshold Decision required under §216.3(a)(l) and (2) shall identify those aspects of the project, program or activity for which environmental review will be completed prior to the time financing is authorized. It shall also include those subprojects or aspects for which environmental review will be deferred, stating the reasons for deferral and the time when environmental review will be completed. Further, it shall state how an irreversible commitment of funds will be avoided until environmental review is completed. The A.I.D. officer responsible for making environmental decisions for such projects, programs or activities shall also be identified (the same officer who has decision-making authority for the other aspects of implementation). This deferral shall be reviewed and approved by the officer making the Threshold Decision and the officer who authorizes the project, program or activity. Such approval may be made only after consultation with the Office of General Counsel for the purpose of establishing the manner in which conditions precedent to disbursement or covenants in project and other agreements will avoid an irreversible commitment of resources before environmental review is completed.

(8) Monitoring. To the extent feasible and relevant, projects and programs for which Environmental Impact Statements or Environmental Assessments have been prepared should be designed to include measurement of any changes in environmental quality, positive or negative, during their implementation. This will require recording of baseline data at the start. To the extent that available data permit, originating offices of A.I.D. will formulate systems in collaboration with recipient nations, to monitor such impacts during the life of A.I.D.'s involvement. Monitoring implementation of projects, programs and activities shall take into account environmental impacts to the same extent as other aspects of such projects, programs and activities. If during implementation of any project, program or activity, whether or not an Environmental Assessment or Environmental Impact Statement was originally required, it appears to the Mission Director, or officer responsible for the project, program or activity, that it is having or will have a significant effect on the environment that was not previously studied in an Environmental Assessment or Environmental Impact Statement, the procedures contained in this part shall be followed including, as appropriate, a Threshold Decision, Scoping and an Environmental Assessment or Environmental Impact Statement.

(9) Revisions. If, after a Threshold Decision is made resulting in a Negative Determination, a project is revised or new information becomes available which indicates that a proposed action might be "major" and its effects "significant," the Negative Determination will be reviewed and revised by the cognizant Bureau and an Environmental Assessment or Environmental Impact Statement will be prepared, if appropriate. Environmental Assessments and Environmental Impact Statements will be amended and processed appropriately if there are major changes in the project or program, or if significant new information becomes available which relates to the impact of the project, program or activity on the

environment that was not considered at the time the Environmental Assessment or Environmental Impact Statement was approved. When ongoing programs are revised to incorporate a change in scope or nature, a determination will be made as to whether such change may have an environmental impact not previously assessed. If so, the procedures outlined in this part will be followed.

(10) Other Approval Documents. These procedures refer to certain A.I.D. documents such as PIDs, PAIPs, PPs and PAADs as the A.I.D. internal instruments for approval of projects, programs or activities. From time to time, certain special procedures, such as those in §216.4, may not require the use of the aforementioned documents. In these situations, these environmental procedures shall apply to those special approval procedures, unless otherwise exempt, at approval times and levels comparable to projects, programs and activities in which the aforementioned documents are used.

(b) Pesticide Procedures.

(1) Project Assistance. Except as provided in §216.3 (b)(2), all proposed projects involving assistance for the procurement or use, or both, of pesticides shall be subject to the procedures prescribed in §216.3(b)(l)(i) through (v). These procedures shall also apply, to the extent permitted by agreements entered into by A.I.D. before the effective date of these pesticide procedures, to such projects that have been authorized but for which pesticides have not been procured as of the effective date of these pesticide procedures.

(i) When a project includes assistance for procurement or use, or both, of pesticides registered for the same or similar uses by USEPA without restriction, the Initial Environmental Examination for the project shall include a separate section evaluating the economic, social and environmental risks and benefits of the planned pesticide use to determine whether the use may result in significant environmental impact. Factors to be considered in such an evaluation shall include, but not be limited to the following:

(a) The USEPA registration status of the requested pesticide;

(b) The basis for selection of the requested pesticide;

(c) The extent to which the proposed pesticide use is part of an integrated pest management program;

(d) The proposed method or methods of application, including availability of appropriate application and safety equipment;

(e) Any acute and long-term toxicological hazards, either human or environmental, associated with the proposed use and measures available to minimize such hazards;

(f) The effectiveness of the requested pesticide for the proposed use;

(g) Compatibility of the proposed pesticide with target and nontarget ecosystems;

(h) The conditions under which the pesticide is to be used, including climate, flora, fauna, geography, hydrology, and soils;

(i) The availability and effectiveness of other pesticides or nonchemical control methods;

(j) The requesting country's ability to regulate or control the distribution, storage, use and disposal of the requested pesticide;

(k) The provisions made for training of users and applicators; and

(l) The provisions made for monitoring the use and effectiveness of the pesticide.

In those cases where the evaluation of the proposed pesticide use in the Initial Environmental Examination indicates that the use will significantly affect the human environment, the Threshold Decision will include a recommendation for the preparation of an Environmental Assessment or Environmental Impact Statement, as appropriate. In the event a decision is made to approve the planned pesticide use, the Project Paper shall include to the extent practicable, provisions designed to mitigate potential adverse effects of the pesticide. When the pesticide evaluation section of the Initial Environmental Examination does not indicate a potentially unreasonable risk arising from the pesticide use, an Environmental Assessment or Environmental Impact Statement shall nevertheless be prepared if the environmental effects of the project otherwise require further assessment.

(ii) When a project includes assistance for the procurement or use, or both, of any pesticide registered for the same or similar uses in the United States but the proposed use is restricted by the USEPA on the basis of user hazard, the procedures set forth in §216.3(b)(1)(i) above will be followed. In addition, the Initial Environmental Examination will include an evaluation of the user hazards associated with the proposed USEPA restricted uses to ensure that the implementation plan which is contained in the Project Paper incorporates provisions for making the recipient government aware of these risks and providing, if necessary, such technical assistance as may be required to mitigate these risks. If the proposed pesticide use is also restricted on a basis other than user hazard, the procedures in §216.3(b)(l)(iii) shall be followed in lieu of the procedures in this section.

(iii) If the project includes assistance for the procurement or use, or both of:

(a) Any pesticide other than one registered for the same or similar uses by USEPA without restriction or for restricted use on the basis of user hazard; or

(b) Any pesticide for which a notice of rebuttable presumption against re-registration, notice of intent to cancel, or notice of intent to suspend has been issued by USEPA,

The Threshold Decision will provide for the preparation of an Environmental Assessment or Environmental Impact Statement, as appropriate (§216.6(a)). The EA or EIS shall include, but not be limited to, an analysis of the factors identified in §216.3(b)(l)(i) above.

(iv) Notwithstanding the provisions of §216.3(b)(l)(i) through (iii) above, if the project includes assistance for the procurement or use, or both, of a pesticide against which USEPA has initiated a regulatory action for cause, or for which it has issued a notice of rebuttable presumption against re-registration, the nature of the action or notice, including the relevant technical and scientific factors will be discussed with the requesting government and considered in the IEE and, if prepared, in the EA or EIS. If USEPA initiates any of the regulatory actions above against a pesticide subsequent to its evaluation in an IEE, EA or EIS, the nature of the action will be discussed with the recipient government and considered in an amended IEE or amended EA or EIS, as appropriate.

(v) If the project includes assistance for the procurement or use, or both of pesticides but the specific pesticides to be procured or used cannot be identified at the time the IEE is prepared, the procedures outlined in §216.3(b)(i) through (iv) will be followed when the specific pesticides are identified and before procurement or use is authorized. Where identification of the pesticides to be procured or used does not occur until after Project Paper approval, neither the procurement nor the use of the pesticides shall be undertaken unless approved, in writing, by the Assistant Administrator (or in the case of projects authorized at the Mission level, the Mission Director) who approved the Project Paper.

(2) Exceptions to Pesticide Procedures. The procedures set forth in §216.3 (b)(l) shall not apply to the following projects including assistance for the procurement or use, or both, of pesticides.

(i) Projects under emergency conditions.

Emergency conditions shall be deemed to exist when it is determined by the Administrator, A.I.D., in writing that:

(a) A pest outbreak has occurred or is imminent; and

(b) Significant health problems (either human or animal) or significant economic problems will occur without the prompt use of the proposed pesticide; and

(c) Insufficient time is available before the pesticide must be used to evaluate the proposed use in accordance with the provisions of this regulation.

(ii) Projects where A.I.D. is a minor donor, as defined in §216.1(c)(12) above, to a multidonor project.

(iii) Projects including assistance for procurement or use, or both, of pesticides for research or limited field evaluation purposes by or under the supervision of project personnel. In such instances, however, A.I.D. will ensure that the manufacturers of the pesticides provide toxicological and environmental data necessary to safeguard the health of research personnel and the quality of the local environment in which the pesticides will be used. Furthermore, treated crops will not be used for human or animal consumption unless appropriate tolerances have been established by EPA or recommended by FAO/WHO, and the rates and frequency of application, together with the prescribed preharvest intervals, do not result in residues exceeding such tolerances. This prohibition does not apply to the feeding of such crops to animals for research purposes.

(3) Non-Project Assistance. In a very few limited number of circumstances A.I.D. may provide nonproject assistance for the procurement and use of pesticides. Assistance in such cases shall be provided if the A.I.D. Administrator determines in writing that

(i) emergency conditions, as defined in §216.3(b)(2)(i) above exist; or

(ii) that compelling circumstances exist such that failure to provide the proposed assistance would seriously impede the attainment of U.S. foreign policy objectives or the objectives of the foreign assistance program. In the latter case, a decision to provide the assistance will be based to the maximum extent practicable, upon a consideration of the factors set forth in §216.3(b)(l)(i) and, to the extent available, the history of efficacy and safety covering the past use of the pesticide the in recipient country.

§216.4 Private applicants.

Programs, projects or activities for which financing from A.I.D. is sought by private applicants, such as PVOs and educational and research institutions, are subject to these procedures. Except as provided in §216.2(b), (c) or (d), preliminary proposals for financing submitted by private applicants shall be accompanied by an Initial Environmental Examination or adequate information to permit preparation of an Initial Environmental Examination. The Threshold Decision shall be made by the Mission Director for the country to which the proposal relates, if the preliminary proposal is submitted to the A.I.D. Mission, or shall be made by the officer in A.I.D. who approves the preliminary proposal. In either case, the concurrence of the Bureau Environmental Officer is required in the same manner as in §216.3(a)(2), except for PVO projects approved in A.I.D. Missions with total life of project costs less than $500,000. Thereafter, the same procedures set forth in §216.3 including as appropriate scoping and Environmental Assessments or Environmental Impact Statements, shall be applicable to programs, projects or

activities submitted by private applicants. The final proposal submitted for financing shall be treated, for purposes of these procedures, as a Project Paper. The Bureau Environmental Officer shall advise private applicants of studies or other information foreseeably required for action by A.I.D.

§216.5 Endangered species.

It is A.I.D. policy to conduct its assistance programs in a manner that is sensitive to the protection of endangered or threatened species and their critical habitats. The Initial Environmental Examination for each project, program or activity having an effect on the environment shall specifically determine whether the project, program or activity will have an effect on an endangered or threatened species, or critical habitat. If the proposed project, program or activity will have the effect of jeopardizing an endangered or threatened species or of adversely modifying its critical habitat, the Threshold Decision shall be a Positive Determination and an Environmental Assessment or Environmental Impact Statement completed as appropriate, which shall discuss alternatives or modifications to avoid or mitigate such impact on the species or its habitat.

§216.6 Environmental assessments.

(a) General Purpose. The purpose of the Environmental Assessment is to provide Agency and host country decision-makers with a full discussion of significant environmental effects of a proposed action. It includes alternatives which would avoid or minimize adverse effects or enhance the quality of the environment so that the expected benefits of development objectives can be weighed against any adverse impacts upon the human environment or any irreversible or irretrievable commitment of resources.

(b) Collaboration with Affected Nation on Preparation. Collaboration in obtaining data, conducting analyses and considering alternatives will help build an awareness of development associated environmental problems in less developed countries as well as assist in building an indigenous institutional capability to deal nationally with such problems. Missions, Bureaus and Offices will collaborate with affected countries to the maximum extent possible, in the development of any Environmental Assessments and consideration of environmental consequences as set forth therein.

(c) Content and Form. The Environmental Assessment shall be based upon the scoping statement and shall address the following elements, as appropriate:

(1) Summary. The summary shall stress the major conclusions, areas of controversy, if any, and the issues to be resolved.

(2) Purpose. The Environmental Assessment shall briefly specify the underlying purpose and need to which the Agency is responding in proposing the alternatives including the proposed action.

(3) Alternatives Including the Proposed Action. This section should present the environmental impacts of the proposal and its alternatives in comparative form, thereby sharpening the issues and providing a clear basis for choice among options by the decision-maker. This section should explore and evaluate reasonable alternatives and briefly discuss the reasons for eliminating those alternatives which were not included in the detailed study; devote substantial treatment to each alternative considered in detail including the proposed action so that reviewers may evaluate their comparative merits; include the alternative of no action; identify the Agency's preferred alternative or alternatives, if one or more exists; include appropriate mitigation measures not already included in the proposed action or alternatives.

(4) Affected Environment. The Environmental Assessment shall succinctly describe the environment of the area(s) to be affected or created by the alternatives under consideration. The descriptions shall be no longer than is necessary to understand the effects of the alternatives. Data and analyses in the Environmental Assessment shall be commensurate with the significance of the impact with less important material summarized, consolidated or simply referenced.

(5) Environmental Consequences. This section forms the analytic basis for the comparisons under paragraph (c)(3) of this section. It will include the environmental impacts of the alternatives including the proposed action; any adverse effects that cannot be avoided should the proposed action be implemented; the relationship between short-term uses of the environment and the maintenance and enhancement of long-term productivity; and any irreversible or irretrievable commitments of resources which would be involved in the proposal should it be implemented. It should not duplicate discussions in paragraph (c)(3) of this section. This section of the Environmental Assessment should include discussions of direct effects and their significance; indirect effects and their significance; possible conflicts between the proposed action and land use plans, policies and controls for the areas concerned; energy requirements and conservation potential of various alternatives and mitigation measures; natural or depletable resource requirements and conservation potential of various requirements and mitigation measures; urban quality; historic and cultural resources and the design of the built environment, including the reuse and conservation potential of various alternatives and mitigation measures; and means to mitigate adverse environmental impacts.

(6) List of Preparers. The Environmental Assessment shall list the names and qualifications (expertise, experience, professional discipline) of the persons prima-

rily responsible for preparing the Environmental Assessment or significant background papers.

(7) Appendix. An appendix may be prepared.

(d) Program Assessment. Program Assessments may be appropriate in order to assess the environmental effects of a number of individual actions and their cumulative environmental impact in a given country or geographic area, or the environmental impacts that are generic or common to a class of agency actions, or other activities which are not country-specific. In these cases, a single, programmatic assessment will be prepared in A.I.D./Washington and circulated to appropriate overseas Missions, host governments, and to interested parties within the United States. To the extent practicable, the form and content of the programmatic Environmental Assessment will be the same as for project Assessments. Subsequent Environmental Assessments on major individual actions will only be necessary where such follow-on or subsequent activities may have significant environmental impacts on specific countries where such impacts have not been adequately evaluated in the programmatic Environmental Assessment. Other programmatic evaluations of class of actions may be conducted in an effort to establish additional categorical exclusions or design standards or criteria for such classes that will eliminate or minimize adverse effects of such actions, enhance the environmental effect of such actions or reduce the amount of paperwork or time involved in these procedures. Programmatic evaluations conducted for the purpose of establishing additional categorical exclusions under §216.2(c) or design considerations that will eliminate significant effects for classes of actions shall be made available for public comment before the categorical exclusions or design standards or criteria are adopted by A.I.D. Notice of the availability of such documents shall be published in the Federal Register. Additional categorical exclusions shall be adopted by A.I.D. upon the approval of the Administrator, and design consideration in accordance with usual agency procedures.

(e) Consultation and Review.

(1) When Environmental Assessments are prepared on activities carried out within or focused on specific developing countries, consultation will be held between A.I.D. staff and the host government both in the early stages of preparation and on the results and significance of the completed Assessment before the project is authorized.

(2) Missions will encourage the host government to make the Environmental Assessment available to the general public of the recipient country. If Environmental Assessments are prepared on activities which are not country specific, the Assessment will be circulated by the Environmental Coordinator to A.I.D.'s Overseas Missions and interested governments for information, guidance and comment and will be made available in the U.S. to interested parties.

(f) Effect in Other Countries. In a situation where an analysis indicates that potential effects may extend beyond the national boundaries of a recipient country and adjacent foreign nations may be affected, A.I.D. will urge the recipient country to consult with such countries in advance of project approval and to negotiate mutually acceptable accommodations.

(g) Classified Material. Environmental Assessments will not normally include classified or administratively controlled material. However, there may be situations where environmental aspects cannot be adequately discussed without the inclusion of such material. The handling and disclosure of classified or administratively controlled material shall be governed by 22 CFR Part 9. Those portions of an Environmental Assessment which are not classified or administratively controlled will be made available to persons outside the Agency as provided for in 22 CFR Part 212.

§216.7 Environmental impact statements.

(a) Applicability. An Environmental Impact Statement shall be prepared when agency actions significantly affect:

(1) The global environment or areas outside the jurisdiction of any nation (e.g., the oceans);

(2) The environment of the United States; or

(3) Other aspects of the environment at the discretion of the Administrator.

(b) Effects on the United States: Content and Form. An Environmental Impact Statement relating to paragraph (a)(2) of this section shall comply with the CEQ Regulations. With respect to effects on the United States, the terms environment and significant effect wherever used in these procedures have the same meaning as in the CEQ Regulations rather than as defined in §216.l(c)(12) and (13) of these procedures.

(c) Other Effects: Content and Form. An Environmental Impact Statement relating to paragraphs (a)(l) and (a)(3) of this section will generally follow the CEQ Regulations, but will take into account the special considerations and concerns of A.I.D. Circulation of such Environmental Impact Statements in draft form will precede approval of a Project Paper or equivalent and comments from such circulation will be considered before final project authorization as outlined in §216.3 of these procedures. The draft Environmental Impact Statement will also be circulated by the Missions to affected foreign governments for information and comment. Draft Environmental Impact Statements generally will be made available for comment to Federal agencies with jurisdiction by law or special expertise with respect to any environmental impact involved, and to public and private organizations and individuals for not less than forty-five (45) days. Notice of availability of the draft Environmental Impact Statements will be published in

the Federal Register. Cognizant Bureaus and Offices will submit these drafts for circulation through the Environmental Coordinator who will have the responsibility for coordinating all such communications with persons outside A.I.D. Any comments received by the Environmental Coordinator will be forwarded to the originating Bureau or Office for consideration in final policy decisions and the preparation of a final Environmental Impact Statement. All such comments will be attached to the final Statement, and those relevant comments not adequately discussed in the draft Environmental Impact Statement will be appropriately dealt with in the final Environmental Impact Statement. Copies of the final Environmental Impact Statement, with comments attached, will be sent by the Environmental Coordinator to CEQ and to all other Federal, state, and local agencies and private organizations that made substantive comments on the draft, including affected foreign governments. Where emergency circumstances or considerations of foreign policy make it necessary to take an action without observing the provisions of §1506.10 of the CEQ Regulations, or when there are overriding considerations of expense to the United States or foreign governments, the originating Office will advise the Environmental Coordinator who will consult with Department of State and CEQ concerning appropriate modification of review procedures.

§216.8 Public hearings.

(a) In most instances A.I.D. will be able to gain the benefit of public participation in the impact statement process through circulation of draft statements and notice of public availability in CEQ publications. However, in some cases the Administrator may wish to hold public hearings on draft Environmental Impact Statements. In deciding whether or not a public hearing is appropriate, Bureaus in conjunction with the Environmental Coordinator should consider:

(1) The magnitude of the proposal in terms of economic costs, the geographic area involved, and the uniqueness or size of commitment of the resources involved;

(2) The degree of interest in the proposal as evidenced by requests from the public and from Federal, state and local authorities, and private organizations and individuals, that a hearing be held;

(3) The complexity of the issue and likelihood that information will be presented at the hearing which will be of assistance to the Agency; and

(4) The extent to which public involvement already has been achieved through other means, such as earlier public hearings, meetings with citizen representatives, and/or written comments on the proposed action.

(b) If public hearings are held, draft Environmental Impact Statements to be discussed should be made available to the public at least fifteen (15) days prior to

the time of the public hearings, and a notice will be placed in the Federal Register giving the subject, time and place of the proposed hearings.

§216.9 Bilateral and multilateral studies and concise reviews of environmental issues.

Notwithstanding anything to the contrary in these procedures, the Administrator may approve the use of either of the following documents as a substitute for an Environmental Assessment (but not a substitute for an Environmental Impact Statement) required under these procedures:

(a) Bilateral or multilateral environmental studies, relevant or related to the proposed action, prepared by the United States and one or more foreign countries or by an international body or organization in which the United States is a member or participant; or

(b) Concise reviews of the environmental issues involved including summary environmental analyses or other appropriate documents.

§216.10 Records and reports.

Each Agency Bureau will maintain a current list of activities for which Environmental Assessments and Environmental Impact Statements are being prepared and for which Negative Determinations and Declarations have been made. Copies of final Initial Environmental Examinations, scoping statements, Assessments and Impact Statements will be available to interested Federal agencies upon request. The cognizant Bureau will maintain a permanent file (which may be part of its normal project files) of Environmental Impact Statements, Environmental Assessments, final Initial Environmental Examinations, scoping statements, Determinations and Declarations which will be available to the public under the Freedom of Information Act. Interested persons can obtain information or status reports regarding Environmental Assessments and Environmental Impact Statements through the A.I.D. Environmental Coordinator.

(22 U.S.C. 2381; 42 U.S.C. 4332)

Dated October 9, 1980

Joseph C. Wheeler

Acting Administrator

Spelling errors corrected

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ANNEX J: GUIDANCE FOR DEVELOPING SEAS FOR MALARIA VECTOR CONTROL PROGRAMS

NOTE

This *Guidance for Developing SEAs for Malaria Vector Control Programs* is a stand-alone document that has also been included as an Annex to *Management Programs for Malaria Vector Control: Programmatic Environmental Assessment* (the PEA). As a result, it refers to the PEA as a separate document, even though it is here an Annex to the PEA.

INTRODUCTION

BEFORE READING THIS DOCUMENT

If you are a prospective preparer of Supplemental Environmental Assessments (SEAs) for malaria vector control programs, it is **essential** that you read the following resources prior to reading this document:

- USAID (Agency for International Development). 2005a. *Environmental Compliance Procedures, Title 22 Code of Federal Regulations, Part 216*. Available at http://www.usaid.gov/our_work/environment/compliance/ reg216.pdf.
- USAID (Agency for International Development). 2005b. *USAID Environmental Procedures Training Manual.* Available at http://www.encapafrica.org/ EPTM.htm.
- USAID (Agency for International Development). 2006. *Management Programs for Malaria Vector Control: Programmatic Environmental Assessment.*
- USAID (Agency for International Development). 2002. *Programmatic Environmental Assessment for Insecticide-Treated Materials in USAID Activities in Sub-Saharan Africa.*

These documents provide in-depth information about environmental compliance procedures in the U.S. Agency for International Development (USAID) and context for this guidance document.

THE SEA: PART OF USAID ENVIRONMENTAL COMPLIANCE

Under the U.S. Code of Federal Regulations (22 CFR §216), malaria vector control activities supported or planned by USAID must undergo environmental examination. To assist USAID missions in planning malaria vector control interventions, USAID recently drafted a Programmatic Environmental Assessment (PEA), *Management Programs for Malaria Vector Control: Programmatic Environmental Assessment* (USAID, 2006), that provides a broad view of the human health and environmental impacts that could result from implementation of malaria vector control interventions. However, the PEA cannot account for intercountry and interregional variation regarding issues such as the capacity to manage pesticides used for vector control and the environment likely to be impacted. For this reason, SEAs must be developed to describe in-country impacts of interventions and describe country-specific activities to minimize those impacts.

Whenever an in-country malaria vector control activity involves "assistance for the procurement or use, or both, of pesticides," SEAs supplementing the PEA must address the Pesticide Procedures found in 22 CFR §216.3 (b). The Pesticide Procedures list 12 factors to address in SEAs and are described in the following chapters.

In sum, the SEA should be looked upon as the overall picture within the country. The SEA should address the human health and environmental impacts that may occur as a result of USAID support of malaria vector control activities.

WHEN TO PREPARE AN SEA

The Bureaus within USAID have different interpretations of 22 CFR §216 and require different types of environmental documentation depending on the type of intervention. *It is important to consult with*

the Bureau Environmental Officer about his or her expectations prior to development of the environmental assessment. Because the majority of USAID-supported malaria interventions occur in Africa, this section will discuss the types of environmental assessments that need to be conducted for various types of malaria vector control interventions.

Within the Africa Bureau, there are essentially two types of environmental assessments:

- *Pesticide Evaluation Report and Safer Use Action Plan (PERSUAP)*—A PERSUAP is written when a Negative Determination is made conditional upon addressing the 22 CFR §216.3 (b) Pesticide Procedures
- *Supplemental Environmental Assessment (SEA)*—An SEA, which by law requires public comment, is written when a Positive Determination is made.

The Africa Bureau generally makes a Positive Determination for malaria vector control activities when

- There are multiple integrated vector management (IVM) interventions
- Environmental Management intervention is used exclusively
- Interior residual spraying (IRS) is used exclusively, using pesticides not registered by the U.S. Environmental Protection Agency (EPA) for health or environmental reasons; all pesticides must be World Health Organization (WHO)-recommended
- IRS is used exclusively, using a mixture of pesticides registered and not registered by EPA (for health or environmental reasons); all pesticides must be WHO-recommended.

The Africa Bureau generally makes a Negative Determination with Conditions for malaria vector control activities when

- IRS is used exclusively, using pesticides registered by EPA; all pesticides must be WHO-recommended
- Insecticide-treated nets (ITNs)/insecticide-treated materials (ITMs) are used exclusively
- Larviciding is used exclusively.

WHO PREPARES AN SEA

SEAs should be prepared during the initial planning stages of one or more interventions in-country, preferably before an intervention or pesticide has been chosen, to provide input in the decision-making process. The individual preparing the SEA can be an employee of the contractor implementing the intervention or an independent contractor.

The individual preparing the SEA should be well acquainted with the possible human health and environmental impacts of the intervention and best-practices to mitigate those impacts. This individual also needs sufficient experience with interpretation and implementation of USAID environmental procedures and with the environmental review process. The SEA preparer will be aided substantially by guidance provided in the *Management Programs for Malaria Vector Control: Programmatic Environmental Assessment* (USAID, 2006).

The SEA preparer should conduct his or her work in conjunction with specialists in the various interventions considered, the logistical needs assessor, host-country malaria control program staff, any regional or local health program staff, and other stakeholders affected by the interventions considered. Specialists should furnish details about the design and implementation of their respective interventions. It is especially important for the SEA preparer and logistical needs assessor to work together so monitoring, mitigation, and evaluation activities can be incorporated into overall project planning.

The USAID Mission health team and the USAID Mission Environmental and Health Officers (MEO and MHO) should be actively involved in the preparation of the SEA. This can be achieved by accompanying the SEA preparer on site visits and participating in discussions, or simply posing questions or making comments or suggestions when the SEA is initially drafted. Once the SEA has been drafted, it must be signed off upon by the Mission Environmental Officer (MEO), Regional Environmental Officer (REO), and the Global Health Bureau Environmental Advisor (BEO).

COMPONENTS OF AN SEA

22 CFR §216.6 (c) describes the content and form that should be used for all USAID environmental assessments, including SEAs. The following sections examine each component of the SEA in detail. The text boxes in each section contain the CFR text. These are followed by discussion of what the section should contain to comply with CFR text and address malaria-specific issues. When relevant, the section will provide additional guidance for on-the-ground research.

ACRONYMS

For most readers, it is helpful to have a list of acronyms and abbreviations at the beginning of the SEA.

TABLE OF CONTENTS

A table of contents at the beginning of the document will enable readers to find relevant information quickly.

SUMMARY

> The summary shall stress the major conclusions, areas of controversy, if any, and the issues to be resolved.

Along with these aspects, the summary may include discussion of the intervention in the context of the timeframe of USAID support, other USAID actions, Ministry of Health initiatives, and the activities of other donors.

BACKGROUND AND PURPOSE

> The Environmental Assessment shall briefly specify the underlying purpose and need to which the Agency is responding in proposing the alternatives, including the proposed action.

To explain the purpose and need for the proposed action, this section should describe the background of malaria and malaria control in the country and the intervention target area. To the extent possible, this section should include information on the following:

- Malaria in the country and intervention target area
  - Malaria parasite species
  - Malaria endemic and epidemic risk areas
  - Start, end, and duration of highest malaria transmission
  - Malaria incidence
  - Malaria prevalence
  - Malaria vector species
- History of malaria control in the country and intervention target area
  - Historical use of insecticides
  - Previous house spraying campaigns
  - ITN distribution targets and mechanisms
  - Previous environmental management campaigns
  - Previous use of larviciding
- Current malaria control policies
  - Interventions supported by the Ministry of Health
  - Rationale for interventions selected
  - Status of intervention implementation or success
  - Pesticide use policies
- Administration of malaria control activities
  - Role of National Malaria Control Program
  - Existence and role of separate department of Vector Borne Diseases
  - Authority of Ministry of Health versus local or regional malaria control programs
- Other donor activities.

Additionally, this section should describe the effectiveness of the malaria interventions already in place and provide some indication of whether they need strengthening through training, better planning, more efficient management, or other processes.

Much of this information can be obtained by talking to national malaria control program staff and browsing relevent documents, such as a national strategic plan for malaria control. Local or regional malaria control program staff may also provide valuable information on the history of malaria and malaria control in the target area and the status of intervention implementation and success.

ALTERNATIVES INCLUDING THE PROPOSED ACTION

This section should present the environmental impacts of the proposal and its alternatives in comparative form, thereby sharpening the issues and providing a clear basis for choice among options by the decision-maker. This section should explore and evaluate reasonable alternatives and briefly discuss the reasons for eliminating those alternatives which were not included in the detailed study; devote substantial treatment to each alternative considered in detail including the proposed action so that reviewers may evaluate their comparative merits; include the alternative of no action; identify the Agency's preferred alternative or alternatives, if one or more exists; and include appropriate mitigation measures not already included in the proposed action or alternatives.

This section is self-explanatory.

AFFECTED ENVIRONMENT

The Environmental Assessment shall succinctly describe the environment of the area(s) to be affected or created by the alternatives under consideration. The descriptions shall be no longer than is necessary to understand the effects of the alternatives. Data and analyses in the Environmental Assessment shall be commensurate with the significance of the impact with less important material summarized, consolidated or simply referenced.

This section overlaps with section (h) in the Pesticide Procedures, which are addressed in Environmental Consequences. When preparing an SEA for an intervention supporting pesticide use, put the information that would be included in this section in the Pesticide Procedures section (see below). When preparing an SEA for environmental management, where pesticides are not used, this section should include the conditions under which the environmental management intervention will take place, including climate, flora, fauna, geography, hydrology, and soils.

The affected environment also includes the human environment. Include information on the administrative divisions in the target area so that when administrative entities are referenced in subsequent sections, they will be familiar to the reader. In addition, include the populations that will be affected by the intervention. The national malaria control program and the local or regional malaria control program can usually provide this information.

ENVIRONMENTAL CONSEQUENCES

This section forms the analytic basis for the comparisons under [Alternatives Including the Proposed Action]. It will include the environmental impacts of the alternatives including the proposed action; any adverse impacts that cannot be avoided should the proposed action be implemented; the relationship between short-term uses of the environment and the maintenance and enhancement of long-term productivity; and any irreversible or irretrievable commitments of resources which would be involved in the proposal should it be implemented. It should not duplicate discussions in [Alternatives Including the Proposed Action]. This section of the Environmental Assessment should include discussions of direct effects and their significance; indirect effects and their significance; possible conflicts between the proposed action and land use plans, policies and controls for the areas concerned; energy requirements and conservation potential of various alternatives and mitigation measures; natural or depletable resource requirements and conservation potential of various requirements and mitigation measures; urban quality; historic and cultural resources and the design of the built environment, including the reuse and conservation potential of various alternatives and mitigation measures; and means to mitigate adverse environmental impacts.

Not every aspect listed here is relevant for malaria vector control interventions. Thus, only the points described below need to be considered.

Any adverse effects than cannot be avoided. For alternatives involving pesticide use, unavoidable adverse effects include human and environmental exposure from emergencies, such as spills or fires, and possible effects from residential or occupational exposure that **cannot** be mitigated. For alternatives involving environmental management, unavoidable impacts on water resources used by humans and other organisms, destruction of flora and fauna, reduction of biodiversity, etc. (see Table 10 in the IVM PEA) should be described here.

Any irreversible or irretrievable commitments of resources. For alternatives involving pesticide use, the Ministry of Health often acquires new insecticides or larvicides, storage facilities, vehicles, application equipment, and protective wear and accoutrements that could be used in future interventions with chemicals that have not undergone environmental review or pilfered and used for activities not related to malaria control, potentially harming human health and the environment.

Discussion of direct and indirect effects and their significance. Direct effects can be characterized as negative and positive. The negative impacts of the intervention are discussed in depth in other parts of the SEA and need only very brief mention here. The positive effects of the intervention, such as providing protection against malaria to a target area population; reduced incidence of adult morbidity, miscarriages, low birth-weight, and adverse effects on malaria-induced fetal neurodevelopment; and reduced incidence of malaria-related childhood anemia, complications, organ failure, and death can be described briefly here.

Indirect effects can be considered equivalent to "irreversible commitments of resources," in that support of malaria vector control interventions may result in procurement of pesticides, equipment, storage facilities, vehicles, or other commodities that can be used for purposes other than those intended or that adhere to best practices.

Conflicts with other policies, plans, or controls for the areas under consideration. It is crucial that malaria vector control interventions supported by USAID do not contradict U.S. or host-country laws, regulations, and policies or international treaties (Stockholm, Basel, Rotterdam) to which the United States or the

host country are party. It is also important to identify whether the proposed action contradicts the goals of other host-country or donor activities in the target area.

Provide an overview of the local environmental and public health regulations as they apply to malaria vector control. This would include any information on

- Pertinent national legislation
- International treaties (Stockholm, Basel, Rotterdam, or other applicable treaties)
- National environmental assessment procedures
- Systems for registration of chemicals
- Guidelines for control operations.

Consult with the Ministry of Health, Ministry of Environment, Ministry of Agriculture, and donor projects to ensure that all aspects of the intervention are legal or complementary to current activities in the target area.

Environmental impacts of the alternatives, including the proposed action. The environmental impacts of alternatives involving pesticide use will be addressed in the Pesticide Procedures (see below). Thus, for alternatives involving pesticide use, simply highlight in this section the primary human health and/or environmental risks of the interventions considered. For alternatives involving environmental management, however, the environmental impacts should be described in depth here.

Pesticide Procedures. 22 CFR 216.3(b) requires that when "a project includes assistance for procurement or use, or both, of pesticides," that the Initial Environmental Examination or subsequent Environmental Assessment address the following 12 factors:

a. The EPA registration status of the requested pesticide
b. The basis for selection of the requested pesticide
c. The extent to which the proposed pesticide use is part of an IVM program
d. The proposed method or methods of application, including availability of appropriate application and safety equipment
e. Any acute and long-term toxicological hazards, either human or environmental, associated with the proposed use and measures available to minimize such hazards
f. The effectiveness of the requested pesticide for the proposed use
g. Compatibility of the proposed pesticide with target and nontarget ecosystems
h. The conditions under which the pesticide is to be used, including climate, flora, fauna, geography, hydrology, and soils
i. The availability and effectiveness of other pesticides or nonchemical control methods
j. The requesting country's ability to regulate or control the distribution, storage, use and disposal of the requested pesticide
k. The provisions made for training of users and applicators
l. The provisions made for monitoring the use and effectiveness of the pesticide.

Guidance on addressing these factors appears in the following chapter of this guidance, Pesticide Procedures.

Recommended mitigation measures. This subsection is the most vital part of the SEA. An SEA is meaningless if the actions recommended are not implemented. This section serves to expedite planning and budgeting for monitoring, mitigation, and evaluation activities. It provides a synopsis of monitoring, mitigation, and evaluation measures that logistical needs assessors, program managers, host-country government staff, and other stakeholders can easily incorporate into project planning. This section should include the type of impact monitored, mitigated, or evaluated and which entity is responsible for the monitoring, mitigating, or evaluating action. Use the recommended mitigation measures in the PEA for IVM (USAID, 2006) and the PEA for ITMs (USAID, 2002) as a guide for recommended mitigation measures in the SEA. Additionally, if pesticide stocks are identified that need to be analyzed and either repackaged or disposed, describe the location of the stocks and the procedures that must be taken to handle those stocks during the program (see the PEA for IVM for the protocol for finding potentially obsolete pesticide stocks).

PREPARATION METHODOLOGY

The Environmental Assessment shall list the names and qualifications (expertise, experience, professional discipline) of the persons primarily responsible for preparing the Environmental Assessment or significant background papers.

In this section, provide a brief methodology for the SEA, including the dates of visits to the host country, names and qualifications of the SEA preparers, and credits to individuals in the host country who provided information for the SEA. If the SEA involved public comment (see Public Comment chapter), provide the date of the scoping meeting, scoping meeting participants, and dates of the host-country public comment period.

BIBLIOGRAPHY

List the resources used in preparing the SEA, such as host country documents and governments, journal articles, United Nations or U.S. best-practice guidelines, the IVM or ITM PEA, or other "significant background papers."

APPENDICES

An appendix may be prepared.

Appendices can be useful in organizing the SEA so that only the most critical information for decision-making is in the body of the SEA. If the SEA involved public comment, include the scoping statement and any public comments on the SEA as appendices.

PESTICIDE PROCEDURES

As previously described, 22 CFR §216.3(b) mandates the consideration of 12 factors when a project includes "assistance for procurement or use, or both, of pesticides." In this chapter, each factor is discussed in sequence. For each factor, a text box highlights the relevent guidance from USAID's *Pest Management Guidelines* (USAID, 1991), and two subsections provide guidance specific to malaria vector control on what to write and how to obtain information required to consider the factor (for some factors, these are presented in a tabular format instead of two subsections, where there is a relationship between what to write and how to obtain information).

(A) THE EPA REGISTRATION STATUS OF THE REQUESTED PESTICIDE

Pesticides are registered in the U.S. by active ingredient and by formulation. "Registration status" possibilities of the active ingredients and the formulated products include registered, never registered, and cancelled.

In the PERSUAP: Identify the registration status in the U.S. and in the host country. Identify the formulated pesticide product to be used.

USAID is effectively limited to using pesticide active ingredients registered in the U.S. by the U.S. Environmental Protection Agency for the same or similar uses. Other pesticides not registered in the U.S. may be authorized, but only if the USAID program can show that no alternatives are available, as required under USAID Pest Management Guidelines for the use on non-U.S. registered pesticides. Host country pesticide registration procedures must also be identified and followed.

What to Write

Essential information includes

- Host-country registration status
- EPA registration status as
  - General Use Pesticide (GUP)
  - Restricted Use Pesticide (RUP)
  - Cancelled (state reasons for cancellation—e.g., health concerns, no market incentive)
- Pesticide formulation and percent of active ingredient
- Registration of any same or similar uses (Note: Larvicides should have same or similar uses in the United States; however, the closest "same or similar use" for insecticides is indoor pest control, because insecticides are not used for IRS or ITN programs in the United States).

Optional information includes

- Chemical Abstracts Service number (CAS number)

- Trade name
- Manufacturer.

Sources of Information

For Host-Country Registration

Each country should have a pesticide registration office. This registration office, typically in the Ministry of Agriculture, may or may not handle the registration of pesticides for *public health* use—sometimes these pesticides are registered by the Ministry of Health. The national malaria control program is likely to know which institution registers public health pesticides.

For EPA Registration

The PEAs for malaria vector control interventions and the PEA for ITMs contain information on EPA registration of WHO-recommended pesticides; if there is a question as to the status of a pesticide, search the EPA website (www.epa.gov) or contact the EPA Office of Pesticides to confirm the current status.

(B) THE BASIS FOR SELECTION OF THE REQUESTED PESTICIDE

This refers to the economic and environmental rationale for choosing a particular pesticide. In general, the least toxic pesticide that is effective is selected.

In the PERSUAP: Explain the basis for selection of the pesticide product to be used, including active ingredient and formulation.

Pesticide product selection may be driven by a number of factors, including efficacy, price, availability, safety, etc. All things being equal, a program should choose the pesticide active ingredient and formulation that presents the least overall risk.

Formulation is a key determinant of toxicity, and should be considered in selecting a particular pesticide product. Formulation can also have an impact on exposure; for example, solid formulations can eliminate the potential for poisoning through accidental exposure to concentrated liquid product.

Packaging can have a significant impact on exposure potential. Large containers necessarily introduce hazardous product transfer steps, as well as the possibility that the product will end up in a smaller, poorly labeled container. Smaller containers are generally better for use in USAID programs.

What to Write

Each SEA should fill include the following table, describing how the following criteria were considered in the host country's decision to use a particular pesticide:

IS THE PESTICIDE…			COMMENTS
Registered by the host country (for public health use)?	YES	NO	If no, describe processes to register the pesticide for the intervention, or reference Pesticide Procedures section (a).
Registered by EPA?	YES	NO	If no, describe why no alternatives exist (e.g.,

IS THE PESTICIDE…			COMMENTS
			need for resistance management, efficacy of pesticide, appropriate wall material), or reference Pesticide Procedures section (a).
WHO-recommended?	YES	NO	If not, USAID should not support the use of this insecticide and should encourage the host-country government to use an alternative insecticide.

IN CHOOSING THE PESTICIDE, DID THE HOST COUNTRY GOVERNMENT CONSIDER…			COMMENTS
Host-country capacity to prevent pilferage	YES	NO	How does your assessment in Pesticide Procedures section (j) compare with the assessment of the decision makers?
Risk to human health	YES	NO	Compare decision-maker's assessment of risk to that in the PEA for IVM. Pilferage can also be considered here.
Risk to environment	YES	NO	Compare decision-maker's assessment of risk to that in the PEA for IVM. Pilferage can also be considered here.
Mosquito resistance	YES	NO	What is the documented vector resistance to the pesticide in the target area? What is the malaria program's policy on resistance management, or switching to different insecticides?
Public knowledge/acceptance of pesticide	YES	NO	Is the public in favor of the pesticide use? For IRS, are refusal rates higher for some insecticides than others?
Cost of pesticide	YES	NO	How do the in-country costs compare? Does this include logistical costs, or not?
Appropriateness for surface spraying (IRS only)	YES	NO	Are the majority of the home interiors in the target area mud, plaster, thatch, wood, coquina, or a combination? What insecticide is most appropriate for this material?

Sources of Information

The person or institution deciding which pesticide to use may include

- Minister of Health
- National malaria program manager

- National malaria program vector control specialist
- A body of key technical experts and stakeholders, such as the National IRS Technical Team in Zanzibar.

Consult individuals involved in pesticide selection to complete the above table.

(C) THE EXTENT TO WHICH THE PROPOSED PESTICIDE USE IS PART OF AN INTEGRATED PEST MANAGEMENT PROGRAM

USAID policy promotes the development and use of integrated approaches to pest management whenever possible. This section discusses the extent to which the proposed pesticide use is incorporated into an overall IPM strategy.

In the PERSUAP: Describe the extent to which the proposed product(s) is/are or could be a part of an IPM program. Describe the connection between the USAID activity and regional, national and local control programs (as appropriate).

Integrated pest management, and its public health counterpart, integrated vector management, is USAID policy because it is the most effective, economical, and safest approach to pest control. "Integrated pest management attempts to control pests in an economically and environmentally rational manner; it emphasizes non-chemical tactics which cause minimal disruption to the ecosystem." USAID programs should assure that the choice of pesticides was made after consideration of other pest management options available, and that this is the most effective and environmentally sound option available.

What to Write

Describe the extent to which the national malaria control program supports the following interventions:

- Environmental management
- Larviciding
- Indoor residual spraying
- Insecticide treated nets.

If the national malaria control program does not support a certain intervention, describe where and when that intervention may be appropriate. Discuss possibilities for combining the goals and regulations of other sectors with those of the malaria control program. For example, Uganda national law mandates that each district conduct sanitation work for public health; such activities could be adapted to reduce vector breeding sites.

Sources of Information

Typically, the national malaria control strategy details the extent to which different vector management options are considered, and target populations or geographic areas that correspond to those options (for example, ITN distribution free of cost to pregnant women and children under 5 years old). Discuss with national and regional or local malaria control program staff the extent to

which the various vector control options are supported, both ideologically and financially. Additional stakeholders, such as public works officers, may provide additional perspectives.

(D) THE PROPOSED METHOD OR METHODS OF APPLICATION, INCLUDING AVAILABILITY OF APPROPRIATE APPLICATION AND SAFETY EQUIPMENT

This section examines in detail how the pesticide is to be applied and the measures to be taken to ensure its safe use.

In the PERSAUP. As stated, describe in detail how the pesticide is to be applied and the measures to be taken to ensure its safe use.

WHAT TO WRITE	SOURCES OF INFORMATION
• General introduction to the intervention; include the purpose for which pesticides are used in that intervention	• PEA and other Environmental Assessments
• Describe the specific method of pesticide preparation and application	• In-field specialist, trainer, IRS program manager, needs assessor, and/or national, regional or local malaria vector control specialists
• Describe the method, duration, and general content of training for workers and supervisors	• In-field specialist, trainer, IRS program manager, needs assessor, and/or national, regional or local malaria vector control specialists
• Describe methods for protecting workers and supervisors from exposure	• PEAs for IVM and ITMs, WHO manuals, industry manuals (see *Resources* chapter)
• Describe method of supervision	• In-field specialist, trainer, IRS program manager, needs assessor, and/or national, regional or local malaria vector control specialists
• Describe how intervention workers and supervisors are chosen	• National malaria control program, local or regional malaria control program

(E) ANY ACUTE AND LONG-TERM TOXICOLOGICAL HAZARDS, EITHER HUMAN OR ENVIRONMENTAL, ASSOCIATED WITH THE PROPOSED USE, AND MEASURES AVAILABLE TO MINIMIZE SUCH HAZARDS

This section of the IEE examines the acute and chronic toxicological data associated with the proposed pesticide. In addition to hazards, this section of the IEE also discusses measures designed to mitigate any identified toxicological hazards, such as training of applicators, use of protective clothing, and proper storage.

In the PERSUAP: Describe measures the program will take to reduce the potential for exposing humans or nontarget organisms to selected pesticides. Also describe monitoring measures that will allow the program to identify problems with users applying other pesticides.

It is recommended that this be the key section of the PERSUAP, in which the majority, or perhaps all, of the planned mitigation measures are described. To address this element, the PERSUAP should summarize the toxicity to humans and other non-target organisms of the pesticide products chosen for the program in question, the potential exposure opportunities presented by those products, and the risk reduction actions the program will take to minimize such exposure opportunities. The risk reduction actions should be described in sufficient detail to show that they are indeed workable solutions. If protective clothing is recommended, for example, assurance should be provided that a sustainable source of such protective clothing has been identified, a schedule for its replacement, training in its use, etc.

WHAT TO WRITE	SOURCES OF INFORMATION
• Acute and long-term toxicological hazards to humans	• Include Pesticide Profile (from Annex E of the PEA for IVM) as an annex to the SEA and reference it
• Steps to prevent occupational exposure	• Reference Pesticide Procedures section (d)
• Steps to prevent residential exposure, typically Information, Education, and Communication (IEC) campaigns through a local subcontractor or local health office	• Methods of communication from local health office or potential subcontractor, critical information content from the PEA for IVM and ITMs
• Steps to mitigate pesticide poisoning, including information provided to target area health practitioners and medicines necessary to procure for treatment	• Target area hospital or health facility manager, Ministry of Health formulary office
• Steps to inform or train drivers transporting pesticide (for long-distance travel and daily operations)	• PEA for IVM

(F) THE EFFECTIVENESS OF THE REQUESTED PESTICIDE FOR THE PROPOSED USE

This section of the PERSUAP requires information similar to that provided in item b, but more specific to the actual conditions of application. This section also considers the potential for the development of pest resistance to the proposed insecticide.

In the PERSUAP: Explain what recommendations or evidence suggests that the ITM products proposed are effective in the program area.

What to Write

- Describe vector resistance to the chosen insecticide or larvicide in the target location, if that information is available
- Describe the impact (or potential impact) of agricultural pesticide use on vector resistance
- Describe steps to ensure quality of the pesticide imported
- Reference Pesticide Procedures section (l) for program monitoring activities that will be conducted to determine pesticide efficacy
- For IRS, describe the insecticide's appropriateness for the wall construction material(s) used in the target location.

Sources of Information

The national malaria control program and the local or regional malaria control program will have information on vector resistance. The Ministry of Agriculture, a local or district agriculture office, or area non-profit organizations may have information on the impact (or potential impact) of agricultural pesticide use. The Ministry of Health or the Ministry of Agriculture should have facilities for testing imported insecticides; if no facilities are available in the host country, ask where pesticides can be tested in the region.

(G) COMPATIBILITY OF THE PROPOSED PESTICIDE WITH TARGET AND NONTARGET ECOSYSTEMS

This section examines the potential effect of the pesticide on organisms other than the target pest (for example, the effect on the bee colonies kept in the area.) Non-target species of concern also include birds and fish. The potential for negative impact on non-target species should be assessed and appropriate steps should be identified to mitigate adverse impacts.

In the PERSAUP. Describe efforts that are being made to minimize environmental exposure to pesticide products.

This section should address the toxicity of the products and the environmental risk mitiation measures that the program will take. The key options for environmental risk mitigation are product choice and exposure reduction. In this section, therefore, describe the relative environmental risk of the product chosen versus the other options. Also describe efforts the program will make to reduce exposure of the environment, through choice of pesticide product and packaging, preparation of eduction materals, training, etc.

This question might also be covered in response to question (e), and if so, simply reference that section without repeating it.

What to Write

- Describe key environmental concerns based on toxicity to non-target organisms and opportunities for negative impacts on non-target organisms typically associated with noncompliance with best practices (for example, pesticide pilferage, locating a storehouse in a flood plain, improper dumping of pesticide in water bodies).
- Describe the steps the program will take to *monitor* and *mitigate* these potential impacts, referencing Pesticide Procedures sections (d) and (e) when appropriate.

Sources of Information

The PEAs on IVM and ITMs indicate toxicity to non-target organisms. Major concerns about how environmental contamination will occur can be discussed with in-field specialists, needs assessor, the program manager, the Ministry of Environment, and the national malaria control program. Typical mitigation and monitoring steps are described in the PEAs on IVM and ITMs.

(H) THE CONDITIONS UNDER WHICH THE PESTICIDE IS TO BE USED, INCLUDING CLIMATE, FLORA, FAUNA, GEOGRAPHY, HYDROLOGY, AND SOILS

This section examines issues such as the potential for contamination of surface and groundwater sources.

In the PERSUAP: Describe the environmental conditions under which the pesticide is to be used, identifying any environmental factors that might be particularly sensitive or subject to contamination from re-treatment operations.

This item refers to particular environmental factors that might accentuate the effects of exposure to pesticides, and the potential need for measures to reduce those risks. Examples of special conditions that need to be noted here include sensitive ecosystems in the project area and superficial groundwater tables.

What to Write

Pertinent information on the target area and corresponding peripheral areas, such as

- Geographic location of target area
- Land area of target location
- Ecological zone
- Climate
- Range and average temperatures
- Range and average rainfall
- Seasonal weather patterns
- Sensitive ecosystems

- Protected areas
- Forest resources
- Common flora and fauna
- Endangered fauna
- Surface water resources
- Groundwater resources (including water table depth, when available)
- Soil types.

Also provide an overview of the monitoring and mitigation efforts to prevent negative environmental impacts.

Sources of Information

General land area maps can be found on the United Nations website or just by searching on the internet. One might expect the Ministry of Environment or a similar ministry to have the information listed above; however, these ministries usually do not have summary information on specific areas in the country. Sometimes the best places to get this information are local environmental non-profit organizations, local donor projects dealing with the environment, or a search on the internet. (An institution may even have geographic information system [GIS] maps containing this information). Surface water resources, groundwater resources, and soil types may also be found this way, although the Ministry of Agriculture may also have this information. Lists of endangered species can be acquired through the World Conservation Union (IUCN) Red List of endangered species.

(I) THE AVAILABILITY AND EFFECTIVENESS OF OTHER PESTICIDES OR NONCHEMICAL CONTROL METHODS

This section identifies other options for control of pests and their relative advantages and disadvantages.

In the PERSUAP: Describe other pest management options being pursued in the geographic area of the activity, either as part of the USAID activity or otherwise, and explain why this particular vector control method was chosen over other available options.

What to Write

- Identify other WHO-recommended chemicals that could be used in the intervention, taking into account host country pesticide laws and regulations
- Describe the potential for using environmental management for malaria vector control, taking into consideration host-country sanitation laws and environmental regulations.

Sources of Information

The Ministry of Agriculture and the Ministry of Health should know which WHO-recommended chemicals are registered in-country and could be used. The Ministry of Health should know what the sanitation laws require and how they can be leveraged to attain malaria control program goals. The Ministry of Environment will know the regulatory constraints on nonchemical approaches to malaria vector control, such as drainage projects, wetland destruction, etc.

(J) THE REQUESTING COUNTRY'S ABILITY TO REGULATE OR CONTROL THE DISTRIBUTION, STORAGE, USE, AND DISPOSAL OF THE REQUESTED PESTICIDE

This section examines the host country's existing infrastructure and human resources for managing the use of the proposed pesticide. If the host country's ability to regulate pesticides is inadequate, the proposed action could result in greater harm to the environment.

In the PERSUAP: Summarize the host country's capacity and structure for the regulation of public health and agricultural pesticides. Identify the approval/registration status of the pesticide product in the host country.

The host country's capacity and structure for the regulation of public health and agricultural pesticides should be summarized. A critical issue for a pesticide activity supported by the Agency is the extent to which the host country's regulatory oversight will help to control distribution, storage, use and disposal of the pesticide products in question. USAID activities should always be in compliance with local environmental and public laws and regulations, but that is not necessarily enough. If host country regulatory systems and institutions are not sufficient to give a reasonable expectation that environmentally sound practices will be enforced, USAID still bears responsibility for assuring environmental protection at each of these steps in the pesticide life cycle.

Government oversight over pesticides is important for controlling the quality of products as well as their environmentally-sound use and disposal. USAID programs of substantial size should generally include an element of capacity-building work with host country institutions that govern public health pesticide use. These measures should be identified in this chapter of the PERSUAP.

WHAT TO WRITE	SOURCES OF INFORMATION
General	
If there are there local, regional, or national laws, regulations, or guidelines on distribution, storage, and disposal of pesticides, describe them and the measures the Program will take to follow those guidelines.	The Ministry of Agriculture and the Ministry of Environment can provide information on national government laws, regulations, and guidelines on pesticide distribution, storage, and disposal.
Describe any capacity-building activities the Program will undertake to improve the host country distribution, storage, and disposal capacity for pesticides.	Discussions with the national malaria control program, the needs assessor, and local and regional officials can elicit suggestions for capacity building for managing distribution, storage, and disposal of pesticides.
Distribution	

WHAT TO WRITE	SOURCES OF INFORMATION
Describe how the pesticide will be transported to the target area.	In-field specialist, IRS program manager, needs assessor, national regional or local malaria vector control specialists
Storage	
Describe the current pesticide storage infrastructure in the target area, and whether the location is sufficient to avoid flooding.	Site visit with needs assessor, and local malaria vector control specialist
Describe the number of storage facilities that are needed for the operation, and where they will be located.	In-field specialist, IRS program manager, needs assessor, national malaria vector control specialists
Describe any construction or renovations that must be undertaken for storage facilities to comply with standards described in UNFAO's Pesticide Storage and Stock Control Manual, including necessary emergency equipment and any need for storekeeper training.	Site visit and UNFAO's Pesticide Storage and Stock Control Manual
Describe measures taken to keep storage facilities secure, such as locating the site in a secure area, double-padlocking, and guarding. Security of storage facilities is vital to preventing pilferage.	In-field specialist, IRS program manager, needs assessor, national malaria vector control specialist, and PEA recommendations
Disposal	
Describe anticipated waste materials from operations, including but not limited to • Insecticide containers, wrappers, and/or sachets • Rinse-water from cleaning personal protective equipment (e.g., overalls, gloves, face shield or mask), sprayers, and spray operators themselves (for IRS).	Pesticide manufacturer, PEA recommendations, in-field specialist, IRS program manager, needs assessor, national malaria vector control specialist
Describe whether or not waste materials are expected to be contaminated with insecticide.	Pesticide manufacturer, in-field specialist, IRS program manager, needs assessor, national malaria vector control specialist
Describe procedures to deal with contaminated materials.	Typically PEA recommendations and UNFAO guidelines; check to make sure any host-country laws and international treaties are followed

(K) THE PROVISIONS MADE FOR TRAINING OF USERS AND APPLICATORS

USAID recognizes that safety training is an essential component in programs involving the use of pesticides. The need for thorough training is particularly acute in developing countries, where the level of education of applicators may typically be lower than in developed countries.

In the PERSUAP: *Describe the provisions made to train and educate those who will be using the pesticides.*

What to Write

Generally describe the training that will be provided to users and applicators. Reference Pesticide Procedures sections (d) and (e).

Sources of Information

Pesticide Procedures sections (d) and (e).

(L) THE PROVISIONS MADE FOR MONITORING THE USE AND EFFECTIVENESS OF THE PESTICIDE

Evaluating the risks and benefits of pesticide use should be an ongoing, dynamic process.

In the PERSUAP: Describe monitoring and evaluation programs for pesticide use activities, and the health and environmental safety-related information that is collected via this M and E capacity.

Monitoring programs should actively investigate, to the extent possible, the following issues:

- Effectiveness of Information, Education and Communication materials and activities in promoting safe handling, use and disposal of pesticide products.
- Adverse health and environmental effects and the frequency and severity with which they occur.
- Quality control of pesticide products.
- Effectiveness of the chosen products and their alternatives, including whether or not resistance is developing.
- Safe and effective pesticide use and handling practices by program staff and end users.

What to Write

Describe the elements of a Human Health and Environmental Evaluation Report (described in the PEA for IVM), their purpose, the activities that must be conducted to achieve that purpose, and the parties responsible for those activities, using the table below as a guide.

Environmental Reporting Elements	Purpose	Activities and Responsible Parties
Post-training evaluation of applicators and supervisors, storekeepers, and medical practitioners	Preliminary assessment of trainees' understanding of training material	Trainers responsible for developing evaluation forms, conducting evaluation, and providing report to program manager and contractor
Post-training evaluation of instructors	Determine effectiveness of training	Program manager responsible for evaluating instructor quality, reporting to contractor
Pesticide stock management reports	Track insecticide leakage/pilferage	Team leaders and supervisors responsible for recording data and submitting it to logistics coordinator or data manager for data aggregation and reporting to program manager and contractor
Mitigation monitoring reports	Identify gaps in implementation of best practices, need for corrective action	Program manager, logistics manager, and/or select supervisors will be responsible for spot-checks of operations. Data manager responsible for synthesizing data and reporting to program manager and USAID Contractor
Environmental impact monitoring reports	Determine whether IRS is exposing sensitive species and ecosystems to pesticide	Contractor or subcontractor responsible for collecting baseline data, intermittent data during and after spray operations, and reporting to the program manager and USAID Contractor
Entomological monitoring reports	Determine effectiveness of IRS on reducing mosquito population	Vector Control Division and National Malaria Control Program of the Ministry of Health
Reports on malaria incidence and morbidity	Determine effectiveness of IRS on reducing malaria incidence and morbidity	Health Center heads are responsible for collecting malaria incidence and morbidity data (baseline and subsequent) and sending it to the District Vector Control officer
		The USAID program data manager and regional or local health office counterpart are responsible for synthesizing data and reporting findings to the program manager and USAID Contractor
Post-intervention survey, assessing knowledge, attitudes, and practices (KAP) of community regarding community roles and responsibilities	Identify information that requires more emphasis or different communication strategy before the next phase or intervention	IEC Subcontractor responsible for survey design, implementation, data analysis, and reporting

The Report may exclude some of these elements, depending on the nature the intervention, the nature of USAID support, the country situation, and USAID and stakeholder concerns.

Sources of Information

The PEA for IVM should be a general guide for monitoring procedures. Details on entomological monitoring can be acquired from the in-field specialist, needs assessor, program manager, or national malaria control program. Environmental monitoring procedures should be determined by a credible host-country institution or other subcontractor.

PUBLIC COMMENT PROCESS

The best resource for explaining the public comment process necessary for SEAs in which a Positive Determination is made is found in USAID's Environmental Procedures Training Manual, Section 3.4, entitled, *What if the IEE results in a Positive Determination?* The details provided in that section will not be repeated here. Instead, the table below provides a brief comparison of the process of preparing an SEA and getting it approved when public comment is required and when it is not.

SEA WITH PUBLIC COMMENT (POSITIVE DETERMINATION)	SEA WITHOUT PUBLIC COMMENT (NEGATIVE DETERMINATION WITH CONDITIONS)
Scoping Process and Statement	Not applicable
Development of Assessment, Pesticide Procedures Included	Development of Assessment, Pesticide Procedures Included
Comment on Assessment by **stakeholders** and USAID, **public meeting in host country**	Comment on Assessment by USAID
Revisions	Revisions
Submission for USAID Approval	Submission for USAID Approval

RESOURCES

This chapter provides a comprehensive list of resources that might be necessary in preparing SEAs or providing guidance to host-country governments on a variety of topics related to malaria vector control and pesticide management.

USAID ENVIRONMENTAL COMPLIANCE

The following documents are essential references for USAID guidance on environmental compliance:

- USAID (Agency for International Development). 2005a. *Environmental Compliance Procedures, Title 22 Code of Federal Regulations, Part 216*. Available at http://www.usaid.gov/our_work/environment/compliance/ reg216.pdf.
- USAID (Agency for International Development). 2005b. *USAID Environmental Procedures Training Manual.* Available at http://www.encapafrica.org/ EPTM.htm.
- USAID (Agency for International Development). 2002. *USAID/AFR Guidance: Preparing PERSUAPs for Pesticide Programs in Africa*. Available at http://www.encapafrica.org/docs/pest-pesticide%20mgmt/PERSUAP%20 Guidance.doc.

STORAGE

Storage capacity and conditions are essential to minimizing exposure, emergencies, and pilferage. All pesticides used for malaria control activities should be stored according to the guidelines in the following manual:

- FAO (Food and Agriculture Organization). 1996. *Pesticide Storage and Stock Control Manual.* FAO Pesticide Disposal Series. Rome.

Additionally, storehouse managers and store-keepers should be trained to manage pesticide stores according to these best practices.

TRANSPORT

Transport of pesticides poses risk of spillage, contamination of the environment, human exposure, and contamination of other transported goods. All pesticides used for malaria control activities should be transported according to the guidelines in the following manual:

- FAO (Food and Agriculture Organization). 1996. *Pesticide Storage and Stock Control Manual.* FAO Pesticide Disposal Series. Rome.

EMERGENCIES AND SPILLS

Mitigation and handling of spill and fire hazards are crucial to preventing human and environmental exposure to pesticides. Of particular concern is inhalation of toxic fumes when pesticides burn in an open flame. Storage facilities should be outfitted for such emergencies, and storehouse managers should be trained in best practices of handling emergency situations according to the guidelines in the following manual:

- FAO (Food and Agriculture Organization). 1996. *Pesticide Storage and Stock Control Manual.* FAO Pesticide Disposal Series. Rome.

Additionally, any fire-fighting or emergency services should be trained on handling pesticide emergencies, and notified immediately when any emergencies occur.

POISON CONTROL

In the event that spray operators or residents experience symptoms of pesticide exposure, treatment should be available and accessible. To that end, physicians in health facilities, health centers, and hospitals should be trained in recognizing and treating poisoning symptoms. Treatment medicines should be available in health facilities, health centers, and hospitals. The following manual should be used to guide training and treatment on pesticide poisoning in malaria vector control programs:

- Reigart JR, Roberts JR. 1999. *Recognition and Management of Pesticide Poisonings. 5th Edition.* U.S. Environmental Protection Agency, Washington, DC.

DECONTAMINATION AND DISPOSAL

Proper decontamination and disposal of expired insecticides, contaminated rinse and wash water, and contaminated packaging products is necessary to mitigate human and environmental exposure to pesticides. The following guidelines should be used to choose decontamination and disposal options that suit the host-country situation:

- Thompson, R. 2004. *Guidance Document: The Selection of Waste Management Options for the Disposal of Obsolete Pesticides and Contaminated Materials.* Draft. Food and Agriculture Organization (FAO). Rome.

PESTICIDE APPLICATION EQUIPMENT

Pesticide application equipment (e.g., compression sprayers) should be manufactured according to WHO standards, and safety equipment (e.g., face shield, overalls) should be procured and worn according to WHO standards. The following documents fully describe specifications for pesticide application equipment:

- WHO (World Health Organization). 2000. *Manual for Indoor Residual Spraying—Application of Residual Sprays for Vector Control.* Geneva.

- Najera, J. and Zaim, M. 2002. *Malaria Vector Control: Decision-Making Criteria and Procedures for Judicious Use of Insecticides.* World Health Organization. Geneva.

- WHO (World Health Organization). 1990. *Equipment for Vector Control. 3rd Edition.* Geneva

PESTICIDE QUALITY CONTROL

Pesticide procured for public health use should be tested for quality assurance. Regardless of whether the pesticide is tested in the host country or whether a sample is sent outside the host country, the following specifications should be used to determine the quality of the pesticide:

- WHO (World Health Organization). 2002. *Specifications for Public Health Pesticides.* Geneva.

PESTICIDE LABELS

The durability, design, and information content of pesticide labels are crucial to ensuring safe use of pesticides. Pesticide manufacturers should adhere to the guidelines for pesticide labels contained in the following manual:

- FAO (Food and Agriculture Organization of the United Nations). 1995. *Guidelines on Good Labeling Practice*. Rome.

RESISTANCE MONITORING

Resistance monitoring is crucial to the appropriate selection and targeted use of pesticides for malaria vector control. Resistance monitoring should be conducted according to the following guidelines:

- WHO (World Health Organization). 1998. *Techniques to Detect Insecticide Resistance Mechanisms (Field and Laboratory Manual)*. Geneva.
- WHO (World Health Organization). 1998. *Test Procedures for Insecticide Resistance Monitoring in Malaria Cectors, Bio-efficacy and Persistence of Insecticide-Treated Surfaces*. Report of the WHO Informal Consultation, Geneva, 28039, September 1998. Geneva.

Additionally, resistance management practices should be implemented in malaria vector control programs in accordance with the following guidelines:

- WHO (World Health Organization). 2003. *The Manual for Insecticide Resistance Management in Vectors and Pests of Public Health Importance*. Geneva.

Finally, ministries of health and agriculture should work together to ensure agricultural use of pesticides will not adversely impact vector control efforts, and vice versa.

ADDITIONAL RESOURCES

In addition to the best practices guidelines referenced in the preceding sections, several manuals have been published that may provide further guidance for malaria vector control strategies involving pesticides:

Chavasse, D. and Yap, H. 1997. *Chemical Methods for the Control of Vectors and Pests of Public Health Importance*. Geneva.

FAO (Food and Agriculture Organization). 1988. *Post-Registration Surveillance and Other Activities in the Field*. Rome.

FAO (Food and Agriculture Organization). 1988. *Guidelines for the Retail Distribution of Pesticides with Particular Reference to Storage and Handling at Point of Supply to Users in Developing Countries*. Rome.

FAO (Food and Agriculture Organization). 1990. *Personal Protection When Working with Pesticides in Tropical Climates*. Rome.

FAO (Food and Agriculture Organization). 1991. *Initial Introduction and Subsequent Development of a Simple National Pesticide Registration and Control Scheme*. Rome.

FAO (Food and Agriculture Organization). 1994. *Provisional Guidelines on Tender Procedures for the Procurement of Pesticides*. Rome.

FAO (Food and Agriculture Organization). 1995. *Disposal of Bulk Quantities of Obsolete Pesticides in Developing Countries*. Rome. (Note: this is guidance for governments.)

FAO (Food and Agriculture Organization). 2002. *International Code of Conduct on the Distribution and Use of Pesticides (Revised Version)*. Rome.

FAO (Food and Agriculture Organization). 2002. *Manual on Development and Use of UNFAO and WHO Specifications for Pesticides*. Plant Production and Protection Paper No. 173. Rome.

FAO (Food and Agriculture Organization), WHO (World Health Organization), and UNEP (United Nations Environment Programme). 1999. *Guidelines for the Management of Small Quantities of Unwanted and Obselete Pesticides*. FAO Pesticide Disposal Series, No. 7. Rome.

Najera, J. and Zaim, M. 2001. *Malaria Vector Control: Insecticides for Indoor Residual Spraying*. Geneva.

United Nations. 2002. *Recommendations on the Transport of Dangerous Goods: Model Regulations*. 10th revised edition. New York.

UNEP (United Nations Environment Programme). 2001. *Stockholm Convention on Persistent Organic Pollutants*. Geneva.

WHO (World Health Organization). 1996. *Report of the WHO Informal Consultation on the Evaluation and Testing of Insecticides*. WHO/HQ, Geneva, 7-11 October 1996. Geneva.

WHO (World Health Organization). 1997. *Guidelines for Poison Control*. Geneva.

WHO (World Health Organization). 1997. *Report of the First WHOPES Working Group Meeting*. WHO/HQ, Geneva, 26–27 June 1997.

WHO (World Health Organization). 1998. *Review of Alpha-Cypermethrin 10% SC and 5% WP and Cyfluthrin 5% EW and 10% WP*. Report of the Second WHOPES Working Group Meeting: WHO/HQ, Geneva, 22–23 June 1998.

WHO (World Health Organization). 1999. *Review of Deltamethrin 1% SC and 25% WT and Etofenprox 10% EC and 10% EW*. Report of the Third WHOPES Working Group Meeting: WHO/HQ, Geneva, 23–24 September 1999.

WHO (World Health Organization). 1999. *Safe and Effective Use of Household Insecticide Products: Guide for the Production of Educational and Training Materials*. Geneva.

WHO (World Health Organization). 2000. *Guidelines for the Purchase of Public Health Pesticides*. Geneva.

WHO (World Health Organization). 2001. *Information, Education and Communication: Lessons from the Past, Perspectives for the Future*. Occasional paper. Geneva.

WHO (World Health Organization). 2001. *Chemistry and Specification of Pesticides*. Sixteenth Report of the WHO Expert Committee on Vector Biology and Control. WHO Technical Report Series No. 899. Geneva.

WHO (World Health Organization). 2001. *Review of IR3535, KBR 3023, (RS)-Methoprene 20% EC, Pyriproxyfen 0.5% GR, and Lambda-Cyhalothrin 2.5% CS*. Report of the Fourth WHOPES Working Group Meeting, WHO/HQ, Geneva, 4–5 December 2000.

WHO (World Health Organization). 2001. *Review of Olyset Net and Bifenthrin 10% WP*. Report of the Fifth WHOPES Working Group Meeting: WHO/HQ, Geneva, 30–31 October 2001.

WHO (World Health Organization). 2003. *Spray Space Application of Insecticides for Vector and Public Health Pest Control—A Practitioners Guide*. Geneva.

WHO (World Health Organization). 2003. *Draft Guidelines on the Management of Public Health Pesticides*. Report of the WHO Interregional Consultation, Chiang Mai, Thailand, 25–28 February 2003. Geneva.

WHO (World Health Organization). 2005. Recommended Classifications of Pesticides by Hazard: Guidelines to Classification 2004. Geneva.

ANNEX K: RECOMMENDED IRS MITIGATION MEASURES

POTENTIAL NEGATIVE ACTIVITIES/IMPACTS	RECOMMENDED MITIGATION ACTIONS
Decreased effectiveness of insecticide, lessening impact on malaria incidence	Laboratory testing of insecticides for IRS to ensure quality control
Occupational risks for workers involved in IRS campaigns (e.g., risks from inhalation, dermal, and oral exposures; vehicular accidents), with particular attention to women of child-bearing age	Pre-contract inspection and certification of vehicles used for pesticide or spray team transport
	Driver training
	Cell phone, PPE, and spill kits on board during pesticide transportation
	Initial and 30-day pregnancy testing for female candidates for jobs with potential pesticide contact; Ensure that pregnant or breast-feeding women are not hired as spray operators, or are re-assigned to non-exposure positions if they become pregnant
	If DDT is used: Prohibit hiring women of child-bearing age as spray operators
	Health fitness testing for all operators
	Procurement of, distribution to, and training on the use of PPE for all workers with potential pesticide contact
	Training on mixing pesticides and the proper use and maintenance of spray pumps, including recognition of insecticide-poisoning symptoms
	Training of health workers in insecticide-poisoning treatment, and provision of antidotes
	Provision of adequate facilities and supplies for end-of-day cleanup, enforcement of clean-up procedures
Safety risks for residents of sprayed houses (e.g., risks from inhalation, dermal, and oral exposures)	IEC campaigns to inform homeowners of responsibilities and precautions
	Prohibition of spraying houses that are not properly prepared (e.g., where food and utensils have not been removed, etc.)
	Two hour exclusion from house after spraying
	Instruct homeowners to wash itchy skin and go to health clinic if symptoms do not subside
Reduced efficacy of IRS insecticides due to improper storage and pilferage of insecticides and consequential human and environmental exposure	Adhere to PMI BMPs for pesticide storage (e.g., watertight roofing, located at least 30 meters from flood plains, wetlands, and water bodies, markets, schools, dwellings, beehives, and protected areas, etc.)
	Adhere to PMI BMPs for warehouse/storage management (e.g., management by trained storekeeper, provision of soap and clean water, etc.)

POTENTIAL NEGATIVE ACTIVITIES/IMPACTS	RECOMMENDED MITIGATION ACTIONS
Ecological risk to non-target species and water bodies from use of insecticides (during mixing and spraying)	Indoor spraying only
	Training on proper spray technique
	If DDT is used: Conduct environmental sampling to monitor DDR residues in affected soil, water bodies, and livestock
	Maintenance of pumps
Environmental risk from disposal of insecticide (both solid and liquid waste)	Choose sites for disposal of liquid wastes according to PMI BMPs
	Construct soak pits with charcoal to adsorb pesticide from rinse water
	Maintain soak pits as necessary during spray season
	Inspect and certify of solid waste disposal sites before spray campaign
	Monitor waste storage and management during campaign
	Monitor disposal procedures post-campaign
Risk of diversion for insecticides for unintended or uncontrolled use	Maintain records of all pesticide receipts, issuance, and return or empty sachets
	Reconciliation of number of houses sprayed versus number of sachets used
	Visual examination of houses sprayed to confirm pesticide application
	Spot checks - occasional physical inventory counts during the spray season
Special precautions	*If malathion or fenitrothion is used*: USAID will discuss the necessity of biomonitoring
	If DDT is used: USAID must ensure that host countries follow the requirements on Parties to the Convention (e.g., notify Stockholm Secretariat and WHO of use of DDT, report use very three years, etc.)

ANNEX L: RECOMMENDED LLIN MITIGATION MEASURES

POTENTIAL NEGATIVE ACTIVITIES/IMPACTS	RECOMMENDED MITIGATION ACTIONS
Environmental impact of procurement of poor quality LLINs leading to need to dispose of nets	Conduct lot testing of LLINs
Misuse of nets (i.e., nets used for non-public health purposes such as fishing)	Procure a quantify of LLINs that considers the ratio of nets to the population, existing supply of nets, and supply of nets from other (non-USAID) sources
	Where there is evidence of misuse for fishing, assess the extent of misuse (tool under development) and collaborate across sectors (Ministries of Health, Environment, and Agriculture) to develop a sustainable, locally relevant solution
Reduced efficacy of LLINs due to improper storage and pilferage of LLINs and consequential human and environmental exposure	Store LLINs in dry, ventilated, and secure facilities to prevent theft or unauthorized access
	Post guard or use barred windows as needed
	Post visible warning signs on doors and windows in local language to alert people that pesticide products are stored inside
	Do not store LLINs with food, feed, or potable water supplies
Worker safety (handling LLINs that are not individually packaged)	Ensure provision of globes and instructions on their use
	Provide worker training on the proper handling of LLINs
Human and environmental impacts of washing LLINs	Ensure that SBCC materials and outreach activities are coordinated with net distribution activities during campaigns, and include guidelines on how to properly wash and maintain LLINs (e.g., discourage disposal of wash water in sensitive ecosystems, discourage washing and rinsing LLINs in water bodies)
Human and environmental impacts of bags and baling materials used to package LLINs	Ensure that SBCC messages inform campaign distributors and local communities about the potential harm to human health and environment if bags and baling materials are reused; support the development of a communication plan that provides messages on best practices for handling and disposing of bags and baling materials.
	In situations where LLIN quality will not be compromised, encourage countries to procure LLINs with minimal packaging (e.g., bulk packaging instead of individually wrapped)
Human and environmental impacts of improper end-of-life disposal	*For countries with policies on end-of-life disposal of nets that involve incineration*: Ensure that incineration of LLINs is conducted in high-temperature incinerators
	For countries with policies on end-of-life disposal of nets that involve burying: Ensure that burial occurs at designated landfills with the following criteria: controlled access, soils with low permeability, away from residences, at least 100 m away from any wells or surface water sources and at

POTENTIAL NEGATIVE ACTIVITIES/IMPACTS	RECOMMENDED MITIGATION ACTIONS
	least 1.5 meters above the water table

ANNEX M: RECOMMENDED LARVICIDAL AGENT MITIGATION MEASURES

POTENTIAL NEGATIVE ACTIVITIES/IMPACTS	RECOMMENDED MITIGATION ACTIONS
Worker safety and human and environmental impact	Develop and implement standard operating procedures (SOPs) for the safe storage and handling of larvicides to prevent loss or leakage.
	Provide training to workers on the SOPs developed for the safe and effective storage of larvicides
	Develop and implement SOPs for the safe distribution of larvicides being transported in bulk in motorized vehicles.
	Provide training to workers and drivers on the SOPs developed for the safe distribution of larvicides
	Develop and implement SOPs for the safe and effective application of larvicides. Application considerations should include: use of appropriate equipment, application techniques and rates, availability and use of PPE, incident reporting, and decontamination procedures.
	Provide training to workers on the SOPs developed for the safe and effective application of larvicides.
	Develop and implement SOPs for properly handling and washing PPE and application equipment.
	Provide training to workers on the SOPs developed for properly handling and washing PPE and application equipment.
	Develop a waste management plan that includes procedures for disposing of larvicide wastes in conformance with international best practices.
	Provide training to workers on the waste management plan for properly handling and disposing of larvicide wastes

ANNEX N - ORGANOPHOSPHATE BIOMONITORING RESULTS

Recommended Citation: PMI Africa IRS (AIRS) Project, Indoor Residual Spraying (IRS) Task Order Six. *Ghana: Piloting Biomonitoring for Pirimiphos Methyl Exposure,* Bethesda, MD, Abt Associates Inc.

Contract: GHN-I-00-09-00013-00

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Prepared by: Abt Associates Inc.

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ACRONYMS

AChE	Acetylcholinesterase
AIRS	Africa IRS
BYD	Bunkpurugu-Yunyoo District
ChE	Cholinesterase
CD	Cholinesterase Depression
COP	Chief of Party
COPIND	Chronic organophosphate–induced neuropsychiatric disorder
EMD	East Mamprusi District
GEMS	Global Environmental Management Support Project
ILO	International Labor Office
IRS	Indoor Residual Spraying
KD	Kumbungu District
MMD	Mamprugu Moaduri District
NMCP	National Malaria Control Program
OP	Organophosphate
PChE	Plasma cholinesterase
PPE	Personal Protective Equipment
PMI	President's Malaria Initiative
RBC	Red blood cells
SOP	Spray Operator
TCPy	Trichloro-2-pyridinol
U.S.	United States
USAID	U.S. Agency for International Development
WHO	World Health Organization
WMD	West Mamprusi District

INTRODUCTION

The President's Malaria Initiative (PMI) has been on the front line of global malaria control efforts since its launch in 2005. Indoor residual spraying (IRS) is one of the cornerstone vector control strategies PMI currently uses in 12 sub-Saharan African countries. Of the four classes of insecticides approved by the World Health Organization (WHO) for use in IRS, malaria vectors have been steadily developing resistance to the formulations used in three out of the four classes. Currently, an organophosphate (OP), Actellic CS, is one of the most effective insecticides in use due to the low level of resistance of the vector and the long-lasting effect of the encapsulated formulation, yet it is also the most expensive.

The latest USAID Programmatic Environmental Assessment (PEA) for Integrated Vector Management Programs for Malaria Vector Control was approved by USAID Bureau Environmental Officers in 2012, and included a clause to pilot biomonitoring if USAID- and PMI-funded programs began utilizing OPs for IRS. In 2012, a longer-lasting OP (pirimiphos methyl, Actellic CS) became commercially available and began to be rolled out in PMI IRS programs. In 2015, Ghana was selected to pilot biomonitoring of seasonal spray workers involved in the application of Actellic CS. PMI and partners, in close collaboration with the National Malaria Control Program (NMCP) of Ghana, developed this pilot to evaluate OP exposure levels in seasonal IRS workers and to determine the feasibility of conducting biomonitoring among spray workers involved in the application of Actellic CS in PMI IRS programs. Data obtained directly from the pilot will help to determine the USAID and PMI policy regarding potential biomonitoring in countries that spray OPs in the future. While PMI piloted a biomonitoring program for Actellic CS, the WHO has determined that biomonitoring of the long-lasting OP (pirimiphos methyl--Actellic CS®) is not required, provided appropriate personal protective equipment (PPE) use (as per the PMI Best Management Practices) and hygiene standards are met.

BACKGROUND

ORGANOPHOSPHATE EFFECT ON ENZYMES

OP compounds owe their insecticidal effect to the inhibition of cholinesterase (ChE) enzyme activity in the nervous tissue. In humans, cholinesterase is important in several nervous system functions. There are different types of ChE in the human body, which differ in their location in the tissue, substrate affinity, and physiological function. The principal ChE's are acetylcholinesterase (AChE), which is present in tissues of the nervous system and in red blood cells (RBC), and plasma cholinesterase (PChE), a group of enzymes present in glial cells, plasma and the liver. The OP compounds can inhibit AChE in an organism; PChE can also be inhibited, but the exact physiological function of PChE is still in doubt (Chen 2015). Congenitally low levels of PChE alone are not associated with functional impairment except when exposed to certain anesthetic drugs (Wong 2000).

OP insecticides inhibit AChE action in nerve synapses, similar to the carbamate class of insecticides. This inhibition of AChE leads to the accumulation of acetylcholine at neuronal junctions, leading to the characteristic symptoms of OP and carbamate overexposure and is the mechanism of toxicity of OPs and carbamates in both humans and pests. OPs inhibit these enzymes through covalent bonding to the enzyme active site, permanently destroying the metabolic activity of the molecule. As a result, the enzyme inhibition is only recovered by the generation of new enzymes. This regeneration occurs in the blood at the rate at which red blood cells are replaced, about 0.8% per day. Carbamate inhibition is temporary and thus dissipates within 24 hours.

AChE, under normal physiological conditions, performs the breakdown of acetylcholine, which is the chemical mediator responsible for physiological transmission of nerve impulses at different sites. In the presence of OPs, AChE is no longer able to break down acetylcholine into choline and acetic acid. The resulting accumulation of acetylcholine in the parasympathetic nerve synapses (muscarinic-like action), the motor end-plate (nicotine-like action) and in the central nervous system is responsible for all typical symptoms occurring after acute OP poisoning, such as excessive sweating, headache, weakness, giddiness, nausea, vomiting, stomach pains, blurred vision, slurred speech, and muscle twitching. (http://www.safeworkaustralia.gov.au/sites/swa/about/publications/pages/hm-organophosphate-2pesticides).

RBC AChE represents the AChE found on RBC membranes, similar to that found in neuronal tissue. Therefore, measurement more accurately reflects nervous system OP AChE inhibition than does measurement of PChE activity. PChE is a liver acute-phase protein that circulates in the blood plasma and is found in the central nervous system's white matter, the pancreas, and the heart. PChE can be affected by many factors, including pregnancy, infection, and medical illness. Additionally, a patient's AChE and PChE activity levels can vary over time in the same individual. One study of unexposed volunteers found an average variability of PChE up to11.5% over a period ranging from 18-247 weeks with similar results observed in AChE variability. However, individual values may vary up to 25% for AChE and 23% for plasma values (Hayes and Laws 1991). RBC AChE is more reflective of the nervous system toxicity of exposure to OP pesticides.

Cholinesterase levels do not always correlate with severity of clinical illness. The rate and the amount of change of AChE in the body are both important in determining whether clinical illness occurs. A more rapid drop in enzymatic activity is more likely to result in illness than a gradual change. Moreover, a variety of conditions can result in falsely reduced ChE levels, both AChE and PChE though rarely are both affected by the same conditions and to the same degree (http://emedicine.medscape.com/article/167726-workup#c6).

EVIDENCE ON EXPOSURE TO ORGANOPHOSPHATES

The acute toxicity of OP pesticides is believed to be exerted through the inhibition of AChE at the synapse, resulting in the accumulation of acetylcholine and overstimulation of responsive tissues such as nerves, glands, and muscles (Costa 2006). There is little dispute about the mechanism of the acute toxicity of OPs, but questions remain about the long term effects on the nervous system after recovery from an acute exposure. Questions also remain regarding the long term effects of lower level non-acute intoxicating exposure to these chemicals.

Exposure to OPs induces several neurological syndromes. The best understood is the acute cholinergic crisis created by the inhibition of AChE at the synapse. Gerhard Shrader invented the insecticides bladin and parathion and the nerve gases tabun, sarin, cyclosarin and soman, and discovered the OP molecule in the years preceding World War II. He is reported to have suffered an acute intoxication by his new invention, leading to his hospitalization. This syndrome characterized by nausea, vomiting, abdominal pain, headache, blurry vision, weakness, sweating, salivation, lacrimation, bronchorrhea and bronchospasm, is a classic intoxication presentation clearly associated with ChE blockade by the OP molecule. A second condition is latent large muscle paralysis, known as intermediate syndrome, which is described in association with recovery from severe acute OP toxicity (Abdollahi et al. 2012). Exposure to other or multiple pesticides have been associated with the development of chronic neurological conditions such as Parkinson's disease or Parkinsonism, but this has not been linked to OP exposure alone (Engel et al 2001).

For many years, human exposure to OP pesticides has been suspected of causing chronic, long lasting central nervous system changes that manifest as behavioral and psychiatric symptoms. As early as the 1950's, clinicians identified the persistence of central nervous system symptoms long after the resolution of acute OP toxicity (Holmes and Gaon, 1956, Tabershaw and Cooper, 1966 Metcalf and Holmes 1969). Also early on, scientists investigated whether chronic exposure to OPs without an acute toxicological event could be responsible for psychiatric symptoms (Gershon and Shaw, 1960). Acute overexposure to OP compounds – which would trigger an illness in a person exposed - has been associated with persistent symptoms of depression, suicidal ideation, and other psychiatric abnormalities as well as decrements in performance on scales for IQ (Savage 1988, Rosenstock 1992). In addition, an extensive review of the neurologic effects of chronic OP pesticide exposure and the epidemiology of suicide pointed out the association between exposure and affective impacts and suggested a connection between chronic OP pesticide exposure and increased rates of suicide (London et al. 2005). It should be noted that the population defined as being chronically exposed to OP pesticides were long-term farmers with variable use of personal protective equipment, which is a very different exposure profile than workers temporarily employed in IRS operations.

Research on sheep dippers exposed to OP in the United Kingdom discovered increased depressive and other neuropsychiatric complaints, consistent with observations that suggest these symptoms appear related to chronic exposure (repeated non-intoxicating exposure over time) to OPs (Buchanan 2001). One of the largest and most precise studies on the subject comes from an ongoing cohort study of pesticide applicators in the United States known as the Agricultural Health Study. Kamel, Engel et al. (2005) reported a significant excess of self-reported neurological symptoms among white male applicators who were classified by their OP use pattern as frequent OP users (as estimated by cumulative lifetime pesticide use), as compared to low frequency users. These symptoms included fatigue, tension, insomnia, depression, difficulty concentrating, loss of appetite, and difficulty speaking. While symptoms were common in all heavy pesticide applicators, those who reported frequent OP use had higher symptom prevalence than other groups. In the same study, and consistent with the observations of others described above, researchers found that female spouses of pesticide applicators were diagnosed more often with depression than their husbands if they had a history of a pesticide poisoning.

A review of the medical literature makes it clear that persistent symptoms, largely of a neurological and/or psychological nature, are associated with an acute OP poisoning event. Much less evidence exists for persistent neurologic symptoms from chronic non-acutely intoxicating OP exposure. Rohlman et al conducted an extensive literature review with a focus on neurobehavioral performance and its association

with occupational OP exposure. She concluded that "There is clear evidence from 19 (of 24) studies that occupational exposure to OPs adversely affects neurobehavioral performance." (Rohlman et al 2011).

CHOLINESTERASE MONITORING: SHOULD BOTH ENZYMES BE USED?

While the acute toxicity of OPs is almost certainly due to the inhibition of AChE at the synapse, humans have two types of ChE circulating in the blood, AChE and butyrylcholinesterase, also known as pseudocholinesterase, serum or plasma cholinesterase (PChE) (Nigg and Knaak 2000). The measurement of these two enzymes has long been used as a method to monitor individuals with exposure to OPs. Both enzymes have been included in the California and Washington State ChE statewide monitoring programs for monitoring exposure among agricultural pesticide applicators (Washington ChE program, California ChE program). While OPs are used in every US state for agriculture, these two states are the only states in the US which currently require employers to make available cholinesterase monitoring for their agricultural workers who handle cholinesterase inhibiting pesticides, although worker participation is not compulsory. To the authors' knowledge, there are no state requirements for non-agriculture workers who use OPs to have cholinesterase testing. The International Labor Office (ILO) identifies the value of both the enzymes in the monitoring of workers with exposure to OP pesticides (International Labor Office 2011). Monitoring the two enzymes has a long history of use as a diagnostic tool to confirm overexposure to OPs. The AChE activity has generally been the more robust and less affected of the two by exposures to OPs. The PChE has been shown to be more easily reduced by exposure to OP than AChE. The results of the two markers used on the same populations do not necessarily correlate and may differ because of the differential effect of the OPs used (Strelitz et al 2014, Mason 1999).

The World Health Organization and other organizations recommend the use of ChE monitoring for some insecticides within the OP class to estimate OP exposure in exposed working populations and several other physiologic parameters have been shown to correlate with either or both ChE tests in field tests of pesticide exposed workers (WHO 1989, Hasin 1999). Nigg and Knaak completed an extensive literature review and identified the value of the two enzymes for worker monitoring (Nigg and Knaak 2000). Trundle et al reviewed and asserted the clinical value of ChE measurements in estimating exposure to OP pesticides (Trundle and Marcial 1988). However, despite the broad acceptance of the use of these two enzymes for monitoring working populations, only a few studies have compared the AChE and PChE results to other markers of exposure. Quandt et al. monitored pesticide exposed farm workers in North Carolina over a season. They measured urinary metabolites and ChE derived from dried blood spots on filter paper and found a significant correlation between the two measures (Quandt et al 2010). Potentially the most valuable work done on the subject to date was recently carried out in Egypt on pesticide applicators applying exclusively chlorpyriphos (Farahat et al). Research showed the correlation between AChE and PChE activities and a unique urinary metabolite of chlorpyriphos, trichloro-2-pyridinol (TCPy). Researchers found a strong correlation between the levels of TCPy in urine and the activity of AChE and PChE as compared to baseline. They reported that "findings in the present study are the first to demonstrate a dose–effect relationship between urinary TCPy concentrations and the inhibition of both plasma PChE and RBC AChE activity in humans occupationally exposed to chlorpyriphos. This dose–effect relationship can be further used to guide future risk assessment efforts for chlorpyriphos exposure." (Farahat et al 2011). Chlorpyriphos is an organophosphate with a mechanism of toxicity similar to Actellic.

What does an isolated depression of PChE mean with respect to the monitoring of health workers? This is not presently answered in the medical literature. The advisory and regulatory institutions which have recommended monitoring workers for exposure to OP pesticides have consistently recommended the monitoring of both AChE and PChE. Their recommendations have not been justified in the documentation available, but scientific literature suggests that the differential effect of some OPs on the two markers justify the use of the two markers. While multiple studies have found that populations working with OPs have demonstrable neurobehavioral deficits, studies have not consistently found an association between these deficits and biomarkers of exposure such as AChE and PChE. Rohlman concluded "Attempts to correlate neurobehavioral deficits with biomarkers of internal dose (urinary metabolites or ChE activity) have been

generally unsuccessful, and a dose-response relationship has yet to be established." (Rohlman et al 2011). A review of the existing literature supports, through example, the use of both tests but does not provide strong scientific justification for the use of both AChE and PChE.

METHODOLOGY

SELECTION OF PILOT SITES AND PARTICIPANTS

Ghana began implementing IRS with the support of PMI in 2008, by spraying five northern region districts. The number of beneficiary districts steadily scaled up to nine by the close of 2011. In 2013, IRS was scaled down to four districts and stayed the same in 2014. PMI began using OPs in Ghana in 2012 as demonstrated in Table 1. In April-May 2015, the PMI-funded AIRS Project implemented an IRS campaign using 16 operational sites across five districts in northern Ghana (Bunkpurugu-Yunyoo District (BYD), East Mamprusi District (EMD), West Mamprusi District (WMD), Kumbungu District (KD), and Mamprugu Moaduri District (MMD)) as shown in Figure 1. Five operational sites, one from each district, were selected for the biomonitoring pilot. In three sites, the project conducted tests at the medical facilities located adjacent to the district operations site. In the other two sites, the project conducted tests at the operations office.

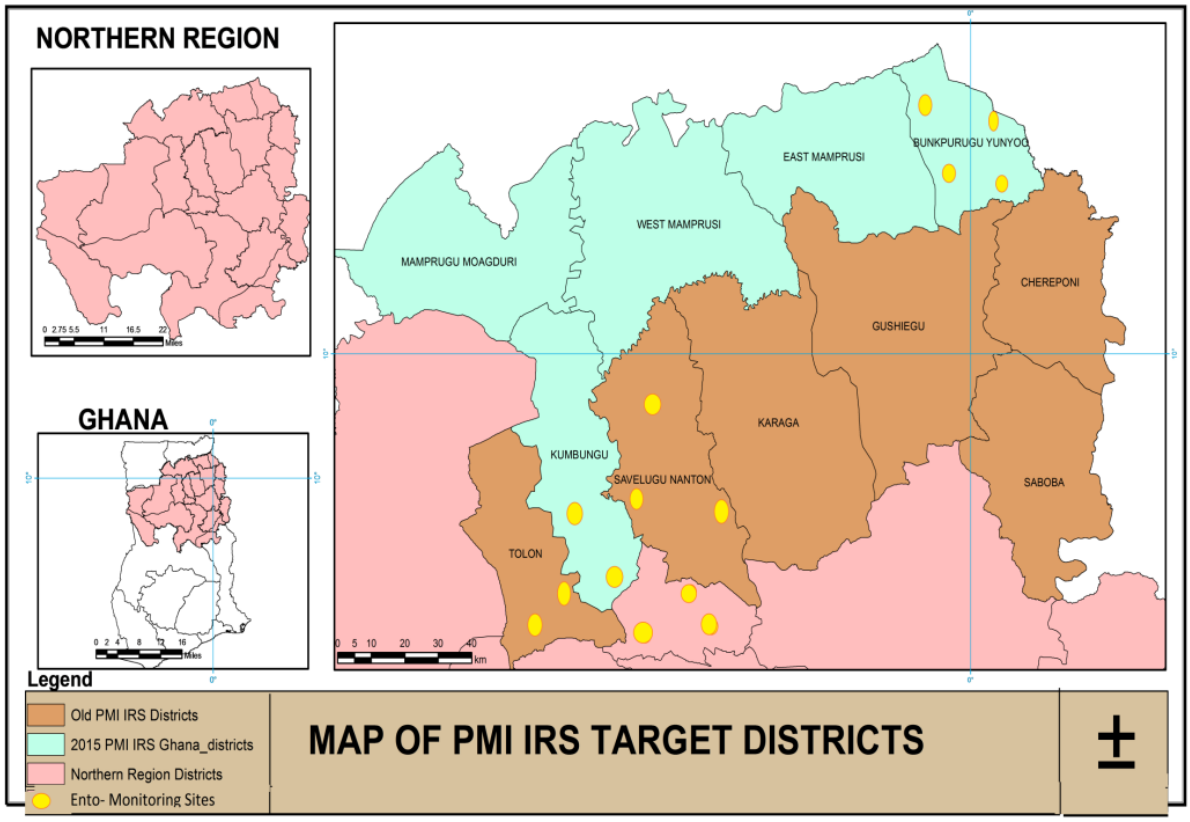
TABLE 1. INSECTICIDES USED FOR IRS IN 2015 PMI SUPPORTED DISTRICTS

District	IRS Campaign Year	Insecticide Used
West Mamprusi*	2008 – 2012 2013 – 2015	Pyrethroids OP
Mamprugu Moaduri*	2008 – 2012 2013 – 2015	Pyrethroids OP
Kumbungu**	2008 – 2011 2012 2013-2014 2015	Pyrethroids OP Not Sprayed OP
East Mamprusi	2009 – 2012 2013 – 2015	Pyrethroids OP
Bunkpurugu-Yunyoo	2011 – 2012 2013 – 2015	Pyrethroids OP

* West Mamprusi was split into two districts, West Mamprusi and Mamprugu Moaduri in 2015

**Tolon-Kumbungu was split into two districts, Tolon and Kumbungu in 2015

FIGURE 1. 2015 PMI SUPPORTED DISTRICTS (IN GREEN)



Criteria for choosing these sites included the number of teams/spray operators (SOPs) working out of each site, presence of a medical facility with competent staff, and site accessibility. The chosen sites also exhibited good geographical dispersion throughout the five districts. All SOPs, team leaders, storekeepers, and washers at a selected biomonitoring site were eligible for testing. Table 2 includes total number and type of workers who participated in the program.

TABLE 2. SITES AND SPRAY PERSONNEL SELECTED FOR BIOMONITORING PROGRAM

District	Site	SOPs		Team Leaders		Washers		Store Keepers		Total		
		F	M	F	M	F	M	F	M	F	M	Total
BYD	Bunkpurugu	13	22	2	5	4	0	1	0	20	27	47
WMD	Janga	7	18	0	5	2	0	1	0	10	23	33
EMD	Gambaga	25	40	6	7	5	0	1	0	37	47	84
MMD	Kubori	6	14	1	3	2	0	0	1	9	18	27
KD	Kumbungu	9	31	2	6	2	0	1	0	14	37	51
Total		60	125	11	26	15	0	4	1	90	152	242

During the recruitment process, AIRS Ghana staff thoroughly explained the biomonitoring program to the SOPs, team leaders, storekeepers, and washers. Those who agreed were asked to sign a participation agreement to that effect.

AIRS Ghana also clarified to the workers that the pilot was a program for assurance monitoring of the effectiveness of PPE specified and used in the PMI IRS program. A consultant hired by PMI through the Global Environmental Management Support (GEMS) project also explained to the supervisors the pilot protocols and conducted training on those protocols. As a monitoring protocol, if a participant's cholinesterase depression (CD) reached a pre-determined action level, the participant was informed of the results as soon as possible, but not later than 48 hours after the test results were obtained. Participants were then removed from the tasks involving possible insecticide contact, re-assigned to another job, and continued to receive their original salary.

BASELINE PLANNING AND TEST KIT

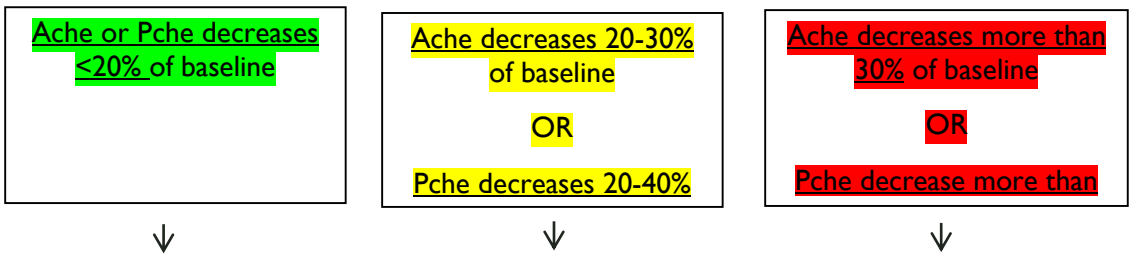
Due to the substantial variability in the "normal" ChE level among individuals, it was necessary to perform baseline testing before the start of spray operations. The baseline tests provided information on each participant's ChE level prior to OP exposure from the IRS campaign. When registering for their baseline test, participants responded to a few questions about the possibility of recent pesticide exposure. Two baseline tests for each participant were conducted three days apart, prior to the start of the IRS campaign. When the results from the two baselines differed by less than 10 percent, an average was used as a reference value for the subsequent follow-up tests. When the difference was greater than 10 percent, the higher of the two values was considered the baseline reference. In this situation, using the highest value provided a more conservative approach.

AIRS determined that the best way to implement this baseline testing was to draw the samples during the mandatory one-week district-based training for all SOPs, team leaders, storekeepers and washers. The first sample was taken on April 8, 2015 and the second on April 11, 2015. Follow-up testing was planned at weekly intervals throughout the five-week spray season.

All follow-up tests were planned for Saturday mornings before work. Qualified medical professionals were responsible for drawing the blood samples and performing the tests. The GEMS consultant trained medical professionals in the performance of their duties on March 31st in Tamale.

AIRS Ghana used *Test-mate EQM*, a test kit, which includes a portable colorimeter to measure both AChE and PChE levels. The test is known to be sensitive to temperature changes (Amaya et al 1996). Ten to 30 degrees Centigrade (50 to 86 degrees Fahrenheit) is the recommended working temperature. To ensure adherence to these parameters, the project procured and installed air conditioners, backup generators, stabilizers and refrigerators for each of the five facilities, stored the test kits in the temperature – controlled room, and allowed the test kits to stabilize to the ambient temperature before beginning the test.

MEASUREMENT CRITERIA



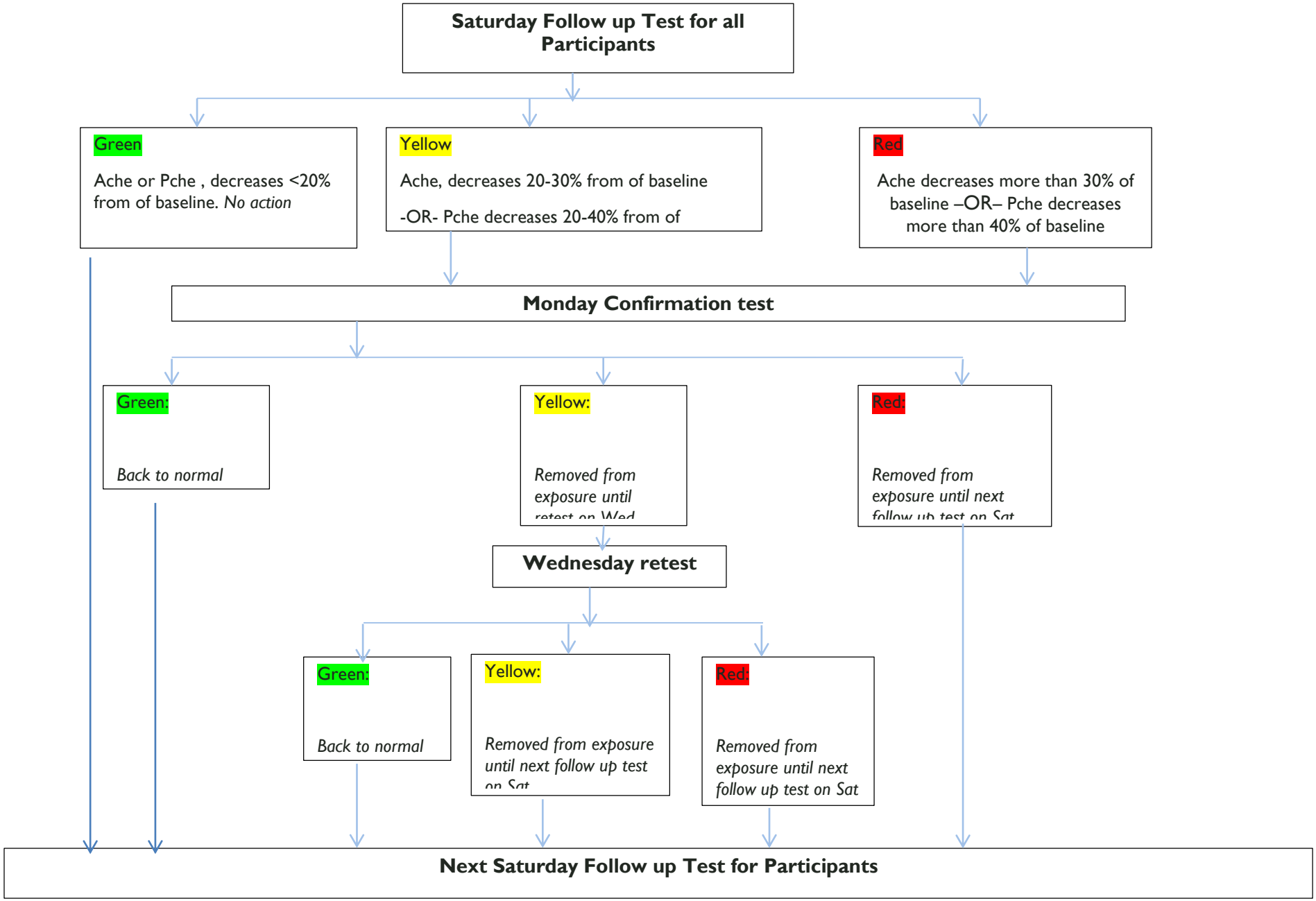
CD was defined as the percentage decrease in ChE activity below a person's baseline levels. The following is a description of the protocol that was used in response to the cholinesterase results of IRS participants:

- Green: When a weekly Saturday measurement of both AChE and PChE shows a decrease of 20 percent or less below baseline values, no action was taken.

- Yellow: When either the AChE or PChE level is decreased by more than 20 percent of baseline, but AChE decreased by less than 30 percent from baseline and PChE decreased by less than 40 percent of baseline, the participant was retested within 48 hours of the follow-up test. An appropriate protocol for action was followed based on the results:
    i. If the Monday morning retest confirmed the depression result, the participant was removed from activities involving potential contact with pesticides. The participant was re-assigned to help the team with mobilization and packing. The district operations coordinator reviewed the condition of the participant's PPE and assessed the person's understanding of personal hygiene requirements and use of PPE. If needed, it included re-training workers on use of PPE.
    ii. If the retest indicated normal levels, the participant received a review of PPE use and the spray protocols, and returned to normal duties.
    iii. All participants confirmed to have CD in the yellow category were retested after two days (on Wednesday) and the same action as above was repeated for those who still experienced CD and those returning to normal levels.
- Red: If AChE level is decreased by more than 30 percent of baseline, or PChE level is decreased by more than 40 percent of baseline, the participant was retested within 48 hours, and if confirmed:
    i. All confirmed reds on Monday (within 48 hours) are removed from spray until the next Saturday test. Those coming to normal will return back to work and those in yellow remain away from spray but doing other tasks for the spray campaign until next Saturday.

All participants with or without any CD during the week were tested every Saturday as a weekly follow-up test. Detailed algorithm of testing calendar is shown in Figure 2.

FIGURE 2. TESTING CALENDAR AND MEASUREMENT CRITERIA



TESTING PROCEDURES

A trained medical professional (laboratory technician) drew the blood sample from each participant with a pinprick. Blood was drawn into two capillary tubes, one for each of the two ChE tests (blood and plasma). A new lancet, alcohol swab, gauze and bandage were used for each individual tested. The samples, after being labeled with a numeric code, were then kept in a refrigerator until processing started immediately after sample collection is completed Sample collection took 1 to 3 hours depending on the number of participants in the site. The participants returned to the operational site to start the spraying work after their blood samples were obtained. After taking all the samples for the day, lab technicians immediately performed the ChE tests. All samples were allowed to warm up to room temperature before processing started. Two data clerks independently recorded the results received from the medical personnel and the double entry was checked for consistency. Two baselines and five follow-up tests were performed for all participants. Participants with CD also took additional confirmatory and retests.

The tests were conducted successfully at all sites. Few sites had power problems during the first day of the baseline test. At KD, testing was interrupted until power was restored and the samples were kept cool in a gas powered refrigerator. At MMD, the collected samples were transported to Tamale in an icebox, and tests were conducted in an air-conditioned room. Power issues in subsequent tests were resolved by purchasing generators as back-up.

MODIFICATION OF THE ORIGINAL PROTOCOL

Following preliminary analysis of the two baseline tests, the project detected that a large proportion (up to 82 percent in one site) of the two pre-exposure baseline values differed from each other by wide margins (20 or more percent). The two baseline values taken at a three-day interval were expected to be similar or narrowly different accounting for variations for tests taken at different times. The most plausible explanation for the discrepancy was that the reagents and buffers purchased in 2014 had been stored in suboptimal conditions and may have degraded. The kits were probably not stored under proper conditions during that entire year. According to the recommendation by the manufacturer, the reagents and buffers should have been kept under 10-30 degree Celsius temperature. There were no temperature records for the room used to store the test items, but temperatures exceed 30 degree Celsius most of the year in this part of Ghana. The reagents in the kits may have undergone some change. Due to the time it takes to bring in new test kits, the IRS stakeholders made a decision against delaying the start of spray operations, and pursued the following course of action:

Fifty spray operators (SOPs) were held back from spraying until the new kits arrived to obtain one pre-exposure baseline for each as a reference value for the follow-up tests. For the remaining 192 participants:

- As the first baseline values, the project used the values that were closer to the one week post-exposure results among the two baseline values obtained using the old kits.
- As the second baseline values, the project used the one week post-exposure values.
- To set one reference value for comparing with the data collected during the follow up tests, the project used the following two approaches to combine the two baseline values:
- If the two baseline values differ from each other by 10 percent or less, the average of the two is taken as the reference value
- If the two baseline values differ from each other by more than 10 percent, the higher of the two is taken as the reference value.

No power problems were encountered during the tests with the new kits and the follow up tests.

ANALYSIS OF DATA

All data from the five follow-up tests, confirmation tests, and retests were collected from the five sites. Results from the individual test results are presented in Section 5. The results for this study are analyzed and discussed in Section 6. In addition to ordinary statistics to analyze trends, the team used two other methods to analyze the collected data: 1) correlation coefficient for Q-values and PChE changes, and 2) linear regression for the effect of proportion of days an SOP used a Hudson pump on the likelihood of being removed from spray operations at any time during the campaign. In Section 5 and 6, all reference to AChE changes are based on the Q-values, which account for any difference in hemoglobin levels of individuals at each testing event, as loss of blood can affect the AChE value. The Q-value for each AChE measured was recorded from the readout on the test machine during testing, but may be estimated as the AChE value divided by the hemoglobin level in g/dL. In Section 6, only the values of the retests are included in the analyses.

After a review of the analysis, 199 participants of the biomonitoring pilot were contacted to provide additional information, including age, experience with IRS, type of spray pumps used, personal use of pesticides, and problems encountered with spray pumps during the campaign. These additional data were used in investigations to characterize the determinants of the recorded CD during the spray campaign.

SUPERVISION OF THE PILOT

The AIRS Ghana Chief of Party (COP) was responsible for the principal oversight of the program to ensure that the program followed stipulated protocols and that all test results were transmitted and reviewed on the same day. An AIRS Ghana staff member was assigned to each of the five sampling sites and supervised sample taking and data entry at each testing center. The GEMS consultant trained one of the AIRS Ghana data entry clerks in each district on data entry and that person performed data recording at each site.

When the day's testing and record-keeping was complete, the site supervisor immediately reviewed the recorded results and handed them over to the data entry clerks. Data entry clerks entered and communicated the data to the COP and supervisors the same day the tests were completed. The COP communicated with the project team members' IRS supervisors if any action was necessary based on the results. An Excel spreadsheet was constructed with cells color-coded according to the test results. This made it easy to see results that required action. Data was communicated to PMI Washington and Ghana teams and the Project home office at Abt Associates within 48 hours.

RESULTS

Among the 242 people eligible to participate, 100% agreed to participate, but 3 missed the testing events (2 after the first follow up and one after the 2nd follow up tests). All 3 were replaced immediately and the replacements were included in the subsequent tests. Reasons for missing the testing included leaving the IRS seasonal work for other opportunities. In BYD, temporary security situations resulted in two participants not accessing the testing center during follow up one.

BASELINE TESTS

Table 3 shows the total number of tests and the number and percentage of cases where the two baseline values varied by more than 20 percent from each other. The number of cases with baseline differences of 20 percent or more was as high as 82 percent and 79 percent in KD and MMD districts respectively. The tests were conducted with old kits. There was no clear pattern of decreasing or increasing values when the second baseline tests were compared with the first baseline tests using the old kits (Table 4).

TABLE 3. BASELINE ONE AND TWO TESTS AND CASES WITH 20% AND HIGHER DIFFERENCE

District	Enzyme	Tests	Number of tests varying by more than 20%	%
KD	AChE	50	41	82
	PChE	51	6	12
MMD	AChE	29	0	0
	PChE	29	23	79
WMD	AChE	31	12	39
	PChE	32	3	9
BYD	AChE	46	2	4
	PChE	46	6	13
EMB	AChE	87	5	6
	PChE	87	18	21
	Total	488	116	24

TABLE 4. SECOND BASELINE PERCENTAGE DIFFERENCE COMPARED TO FIRST BASELINE TESTS WITH THE OLD KITS

Enzyme	Districts				
	KD	MMD	WMD	BYD	EMD
Ache	35.3	5.1	-11.8	5.1	-4.7
Pche	6.6	-29.6	-2.7	1.7	2.1

Pre-exposure baseline tests with new kits for AChE of the 50 selected SOPs were performed on April 16th and 18th: the change in baseline measures taken on these two dates was within the range of -6.9% and 11.1% with an average of 0.5%. One week post-exposure baseline measurements of AChE and PChE for the 192 remaining participants were taken on April 20th. PChE baseline measurements were also taken on April 20th for the 50 SOP kept out of exposure for one week. All protocols for tests were successfully followed.

FOLLOW-UP ONE

The first follow up test for all participants (242) was undertaken on April 25th followed by the confirmation test after 48-72 hours (Monday-Tuesday) and the follow up test for individuals in yellow on Thursday. Table 5 shows the results of these tests. Thirty-eight participants showed mild and 14 participants deeper depression of cholinesterase, resulting in 52 cases of CD. Of these 52 cases, 49 (94.2%) had PChE CD only. Two cases had both PChE and AChE CD and one AChE (red category CD) only. However, upon further examination of the reference baseline values of the three participants with AChE depression, it was clear that one of their baseline AChE values was higher than expected and likely artefactually elevated. It should be noted that there was no indication of AChE depression when the lower baseline AChE value (which may have been the normal AChE value) was considered as a reference against the follow-up results. Therefore, this suggested that all the observed CDs were of PChE

TABLE 5. RESULTS OF FOLLOW-UP ONE TESTS

Districts	Number Tested	1st follow up April 25, Saturday			Confirmation test (48/72 hours) April 27 and 28 (Monday Tuesday)**			Retest for yellows April 30, Thursday		
		Yellow	Red	%	Yellow*	Red	%	Yellow*	Red	%
EMD	84	18	1	23%	8	1	11%	3	1	5%
WMD	35	3	0	9%	2	0	6%	2	0	6%
BYD	43***	3	0	7%	3	0	7%	0	0	0%
MMD	27	5	2	26%	4	3	26%	4	3	26%
KD	51	9	11	39%	9	8	33%	7	8	29%
Total	242	38	14	21%	26	12	16%	16	12	12%

Note: The values in red include some participants moving from yellow to red despite being removed from insecticide exposure.

*are less than the number on Saturday test because some moved to green

**the retest dates do not follow the Mon-Wed schedule for the first follow up, because the Monday tests were missed due to delay in data reporting and analysis

***2 participants missed test due to security reasons

A total of 21 percent of participants had CD during the first follow-up test. After spraying on Saturday and having a break on Sunday, the confirmation test showed that the proportion of people with CD was reduced to 16 percent. During the retest after two days, 10 of the 26 confirmed CD cases in the yellow category returned to normal. Given the CD cases in the red category remained unchanged[1], the total proportion of participants with CD was lowered to 12 percent. The highest numbers of reds were from KD. The possible explanation for this discrepancy is that the district was included in the 2015 campaign after being last sprayed in 2011. Most of the SOPs are new and may not have fully comprehended the requirements for PPE compliance at the start of the IRS campaign. However, close supervision and interviews of the SOPs with CD could not detect any problem with their practice of PPE use.

FOLLOW-UP TWO

The summary of results for follow-up two is shown in Table 6. Fifty-two individuals had CD during the weekly follow-up tests on Saturday. Three of the CD cases in the yellow category were both AChE and PChE

[1] Since these participants were not tested during the retest.

CD. This number was reduced from 52 to 37 during the Monday confirmation test and to 33 during the Wednesday retests for yellows. Most of the reductions represented people in the yellow category returning to normal levels of ChE. However, in MMD, contrary to expectations, four yellows turned to red during the Monday confirmation test and additional one on Wednesday retests. The number of reds in MMD increased from 2 on Saturday to 7 on Wednesday. Overall, the number of red increased from 8 on Saturday to 15 on Wednesday. Participants tested for confirmation on Monday would have sprayed on Saturday with a break on Sunday. The situation of participants moving from yellow to red between Saturday and Monday could be explained as exposure from spraying on Saturday. However, since all participants with CD in the yellow category on Saturday or Monday were removed from spraying, the project did not expect such participants with CD in the red category on the following Wednesday retest to be the result of insecticide exposure. Again, two cases had both AChE and PChE depression and one case had only AChE depression (all in the yellow category) during follow-up two. The case with only AChE depression was the same from follow-up one that did not result in AChE depression when using the lower baseline AChE value (which may have been the normal AChE value). One of the other two cases was also indicated as AChE depression during the follow-up two tests with one new case. There was no indication of AChE depression when the lower baseline AChE value was considered as a reference against the follow-up results. Therefore, this suggested that all the observed CDs were of PChE.

TABLE 6. RESULTS OF FOLLOW-UP TWO TESTS

Districts	Number of Participants	2nd follow up May 2, Saturday			Confirmation May 4, Monday			Retest for yellows May 6, Wednesday		
		Yellow	Red	%	Yellow	Red	%	Yellow	Red	%
EMD	84	17	1	21%	13	0	15%	7	5	14%
WMD	35	4	0	11%	1	0	3%	0	0	0%
BYD	45	5	0	11%	1	0	2%	0	0	0%
MMD	27	9	2	41%	5	6	41%	4	7	41%
KD	51	9	5	27%	8	3	22%	7	3	20%
Total	242	44	8	21%	28	9	15%	18	15	14%

Note: The values in red include some participants moving from yellow to red despite being removed from insecticide exposure.

FOLLOW-UP THREE

Table 7 summarizes the results of follow-up three. Fifty-six participants had CD in the yellow and red categories during the Saturday weekly follow-up testing. One of the cases in the yellow category was from both AChE and PChE CD. This number was reduced from 56 to 44 during the confirmation test on Monday, and to 33 during the retest for yellows on Wednesday. Most of the changes came from people moving from yellow to normal. However, there was little change in the number of cases of CD in the red category. In fact, the number increased from six to ten participants between the confirmation and the retests for only yellow CD cases, despite the fact that the yellows were kept out of contact with the insecticide between Monday and Wednesday. The only case with AChE depression indicated during the follow-up three tests was the case with only AChE depression from the follow-up one and follow-up two tests. When the lower of the two pre-exposure baselines AChE measures was used as the reference, there was no indication of CD for this case.

TABLE 7. RESULTS OF FOLLOW-UP THREE TESTS

Districts	Number of Participants	3rd follow up May 9, Saturday			Confirmation May 11, Monday			Retest for yellows May 13,Wednesday		
		Yellow	Red	%	Yellow	Red	%	Yellow	Red	%
EMD	84	23	0	27%	15	0	18%	12	0	14%
WMD	35	3	0	9%	3	0	9%	2	0	6%
BYD	45	5	2	16%	5	2	16%	2	2	9%
MMD	27	10	2	44%	9	2	41%	6	3	33%
KD	51	8	3	22%	6	2	16%	1	5	12%
Total	242	49	7	23%	38	6	18%	23	10	14%

Note: The values in red include some participants moving from yellow to red despite being removed from insecticide exposure.

FOLLOW-UP FOUR

The Saturday week four follow-up tests showed 65 people with CD; 60 in the yellow category (one of these was both AChE and PChE CD) and five in the red category as demonstrated in Table 8. This number was lowered to 33 during the confirmation check on Monday and then to 20 during the Wednesday retests for yellows only. The week four follow-up test also showed the least number of reds compared to the previous follow-up tests despite the slight increase in the yellows. However, one person moved to the red category from the yellow category during the retests on Wednesday. As expected, most of the reduction in CD was due to people in the yellow category changing status to normal during the confirmation and Wednesday retests. The only case with AChE depression indicated during the follow-up four tests was the case with only AChE depression from the follow-up one, follow-up two, and follow-up three tests. When the lower of the two pre-exposure baseline AChE measures was used as the reference, there was no indication of CD for this case.

TABLE 8. RESULTS OF FOLLOW-UP FOUR TESTS

Districts	Number of Participants	4th follow up May 16 Saturday			Confirmation May 18 Monday			Retest for yellows May 20 Wednesday		
		Yellow	Red		Yellow	Red		Yellow	Red	
EMD	84	26	1	32%	11	0	13%	6	0	7%
WMD	35	4	0	11%	3	0	9%	1	0	3%
BYD	45	13	0	29%	7	1	18%	6	1	16%
MMD	27	6	1	26%	5	1	22%	4	2	22%
KD	51	11	3	27%	5	0	10%	0	0	0%
Total	242	60	5	27%	31	2	14%	17	3	8%

Note: The values in red include some participants moving from yellow to red despite being removed from insecticide exposure.

FOLLOW-UP FIVE

Follow-up five produced the highest number of people with CD; mostly in the yellow category (3 of these were both AChE and PChE CD). Across four sites, there were 68 cases of CD as shown in Table 9. One of the sites was not sampled because spraying finished at the site by follow-up five. However, there was no increase in the number of cases in the red category compared to the previous week of testing. Unlike the previous weeks, no confirmation tests were conducted on Monday because spraying was over and there was no need to remove participants from operation based on their CD results. The last retests were conducted for all participants on Wednesday and the number of people with CD was reduced by more than half. The trend of participants with CD in the yellow category showing CD in the red category in subsequent retests, despite not being involved in spraying activities was again observed in two individuals. Two cases indicated both AChE and PChE depression and one case (same as the four previous follow-up tests) indicated only AChE depression during the follow-up five tests. The two cases of both AChE and PChE depression were both new. When the lower of the two pre-exposure baseline AChE measures was used as the reference, there was no indication of CD for this case.

TABLE 9. RESULTS OF FOLLOW-UP FIVE TESTS

Districts	Number of Participants	5th follow up May 23, Saturday			Follow up for yellows and reds May 27, Wednesday		
		Yellow	Red	%	Yellow	Red	%
EMD	84	26	0	31%	12	2	17%
WMD	0	0	0	0	0	0	0
BYD	45	16	0	36%	7	0	16%
MMD	27	11	4	56%	7	0	26%
KD	51	9	2	22%	3	1	8%
Total	207	62	6	33%	29	3	15%

Note: The values in red include some participants moving from yellow to red despite being removed from insecticide exposure.

Overall, it's important to note that no true case of only AChE depression was observed and there were no clinical symptoms of poisoning in individuals showing PChE depression.

DISCUSSION

As previously stated, the purpose of this pilot was two-fold: (1) to evaluate OP exposure levels in seasonal IRS workers, and (2) to determine the feasibility of conducting biomonitoring among spray workers involved in the application of Actellic CS.

Exposure

All true CDs were due to PChE and none of the participants showed any clinical symptoms of CD or poisoning. AChE measures for six participants indicated CD in 11 instances over the five follow-up tests. In all cases, when the lower of the pre-exposure AChE baseline values was used as the reference, there was no indication of AChE depression. The data suggest that the detections of PChE depression were generally real biological effects rather than only artefactual depressions due to a less than accurate baseline. The strongest evidence for this is that depressed activity, as expected, recovered in the absence of exposure or, when exposures continued, worsened. However, there was no case of symptomatic expression of exposure to pirimiphos-methyl even among cases who recorded PChE depression of the red category. Of the 33 CD cases from the follow-up two tests, 55 percent were new cases, 12 percent were yellow cases that were red cases from the previous test, 9 percent were red cases that were yellow cases from the previous test, and 24 percent were repeat cases. For follow-up three, 57 percent were new cases, 13 percent were yellow cases that were red cases from the previous test, and 30 percent were repeat cases. For follow-up four, 52 percent were new cases, 5 percent were yellow cases that were red cases from the previous test, and 44 percent were repeat cases. For follow-up five, 22 percent were new cases, 3 percent were red cases that were yellow cases from the previous test, and 75 percent were repeat cases.

No case of solely AChE depression was observed and there were no clinical symptoms of poisoning in individuals showing PChE depression. Figure 3 shows the trend in the number of people with PChE CD as the spray campaign progressed. There was a continuous increase in the number of people with mild depression (yellow) as the spray season progressed. On the other hand, the number of CD cases in the red category declined or remained unchanged with time. This might be explained by the fact that the number of people with mild CD increased with the increase in the number of days of exposure as the spray season progressed. Rather than representing a sudden one-time exposure, this may indicate a gradual accumulation of inhibition (inhibition exceeding recovery) from continued exposure. The number of CD cases in the red category was likely not increasing because the red category participants were constantly removed from spray until their PChE levels recovered to less than 20 percent depression compared to their baseline level.

There were unexpected CD cases that moved from the yellow category to the red category during the Monday confirmation and Wednesday retest for cases with CD on the Saturday weekly follow-up tests. The expectation was that CD cases in the yellow category, when given a break from activities related to insecticide handling, would move to the normal group and not to the red category. The yellows that turned to red on the Monday confirmation test may be due to their exposure to insecticides during spray activities the same day after their weekly Saturday test. However, it is unclear why cases changed from yellow to red during Wednesday retest, even after these participants were kept out of activities that exposed them to insecticides.

Several processes may provide insight into this continued depression despite discontinuation of exposure. The first question that must be asked is whether additional exposure is taking place outside of the IRS work. This could be through personal use of insecticide on home farms or gardens. Additionally, it should be investigated as to whether the workers in this category might have used pesticides in the home or whether their own homes were sprayed in the IRS program. It should be noted that SOPs are from the communities sprayed by the program and it is highly likely their houses were also sprayed. We do not know if or how living in a sprayed home affects biomonitoring results. Even the mild exposure sustained in their own homes might be sufficient to move them to a category lower. A study of the toxicity of pirimiphos-methyl on albino rats showed the peak cholinesterase inhibition occurred at 24 hours after administration of an oral dose of the chemical (Rajini and Krishnakumari 1988). The dynamics of the release of activated metabolites from subcutaneous deposition after absorption through dermal exposure (the likely mechanism of exposure in this

worker population) are not fully understood for human beings and it is possible that this delayed peak in cholinesterase inhibition might be even more delayed beyond the 24 hours seen in orally dosed rats. Another consideration is that some foods (including, green potatoes, eggplant, and tomato, which are readily available and usually included in the diet of workers in the region) are known to inhibit cholinesterase to a small degree. Recent work in herbal medicine research has shown that several herbal teas and remedies can inhibit both PChE and AChE as well. Likely many more exist that have not as yet been identified (Liew et al 2014, Adersen et al 2013, Hajimehdipoor et al. 2014). A dietary history could potentially identify such exposures.

Liver disease, pregnancy, hemolysis and certain foods and medicines can inhibit cholinesterase and complete control of these variables was not practical (Hayes and Law 1991).

The indoor residual spraying season generally precedes the period of crop use of agricultural pesticides (which may include organophosphates and or carbamates). Additionally, we did ask whether spraying pesticides had occurred outside of the IRS program. However potential for exposure to our IRS workforce might come about through nonobvious exposure to such chemicals stored in the home.

Finally, if a worker's cholinesterase value is very close to the breakpoint between yellow and red, random biological variation or inherent test error may explain the movement to the red category from the yellow category.

The correlation coefficient for the AChE and PChE changes compared to the baselines of all participants for the five follow up tests was +0.061. A correlation coefficient of ±1 signifies perfect correlation, and a correlation coefficient of 0 signifies no correlation. This indicates that there was close to no relationship between the direction and level of AChE and PChE changes. When AChE and PChE measures for workers, once they have been determined to have CD such that it warranted removal from operations based on the stated protocols, are excluded from the measures, the correlation coefficient increases to +0.073. This is still too low to signify a relationship between the measured AChE and PChE changes.

FIGURE 3. NUMBER OF WORKERS REMOVED FROM OPERATIONS DUE TO CHOLINESTERASE DEPRESSION, FOLLOW-UPS 1-5, ALL DISTRICTS

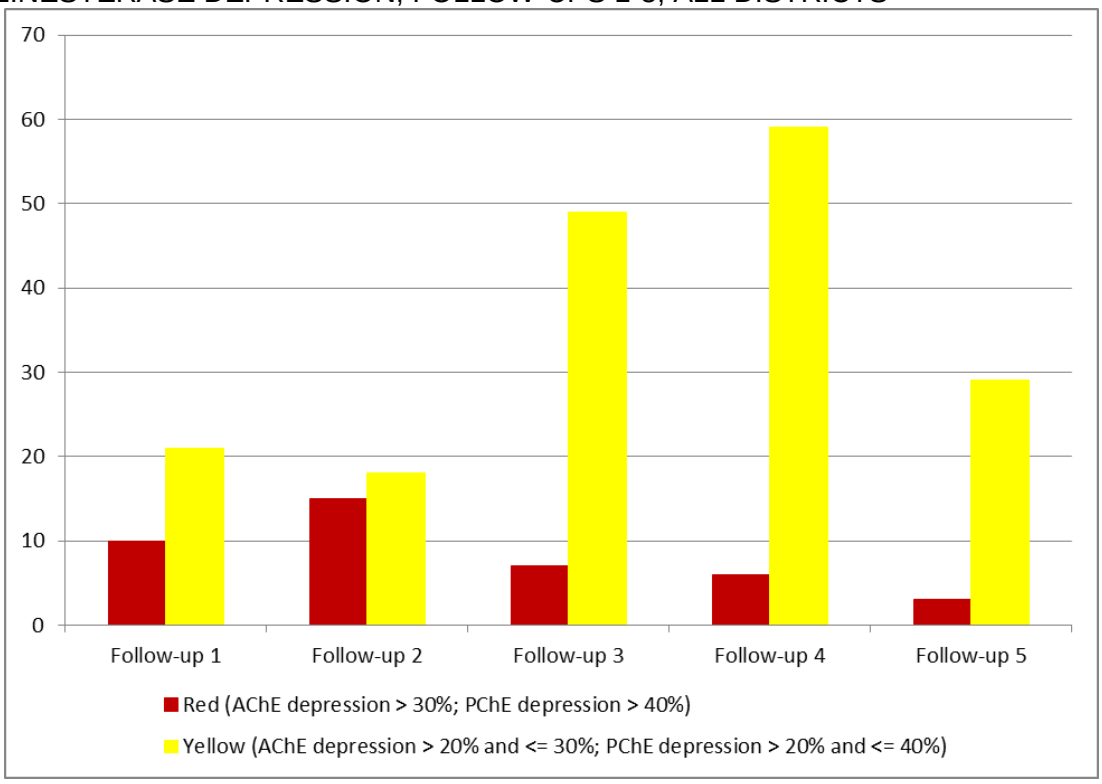
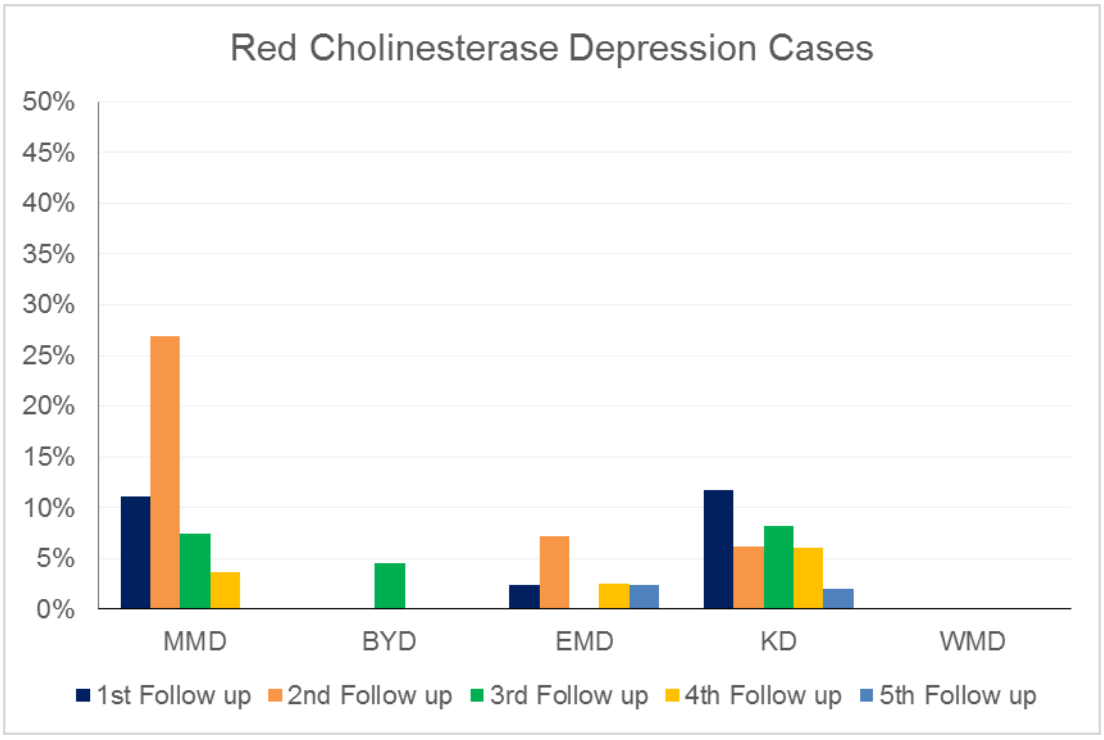
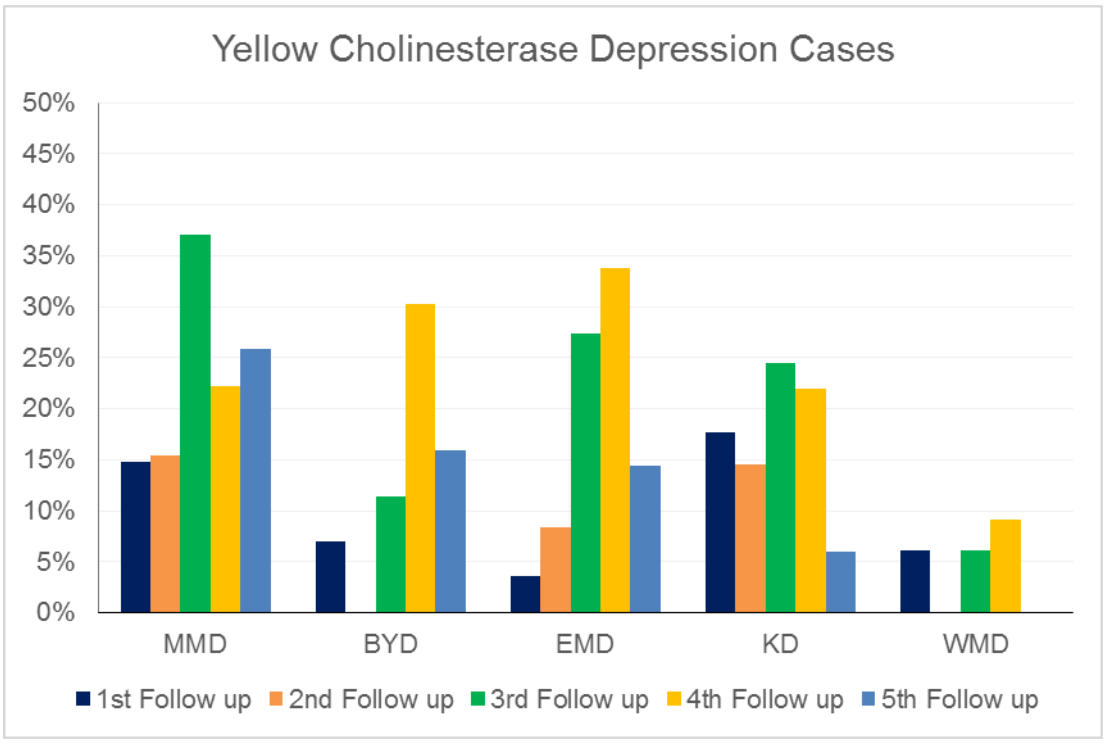


Figure 4 presents the proportion of workers with CD for the five operations sites over the five follow-up tests. These are the CD cases that remained after the Wednesday retest for each week. As presented in Tables 4-8, the majority of CD cases were in the yellow category. As a result, the bars in the lower panel of Figure 4 – representing the number of CD cases in the yellow category for each site – are a lot taller than the corresponding bars in the upper panel. The highest proportions of workers with CD in a given week were recorded in the MMD site, and in all cases, the majority of these CD cases were in the yellow category. The WMD site always had a small proportion of workers (never higher than 10 percent) with CD and none of the CD cases were in the red category.

One possible reason for the lower number of CD of the yellow and red category in the WMD and BYD sites was that only Hudson pumps were used by spray operators at these two sites. Based on a sample of 144 spray operators, who were contacted after the end of spray operations, the probability of not being removed from spray operations at any point during the campaign increased by about 19% with a 1% increase in use of the Hudson pumps. In addition, most of the spray operators at the WMD and BYD sites who were removed from operations at some point in the campaign reported having to fix their pumps between "rarely" and "sometimes", compared with between "sometimes" and "often" for the spray operators at the other three sites.

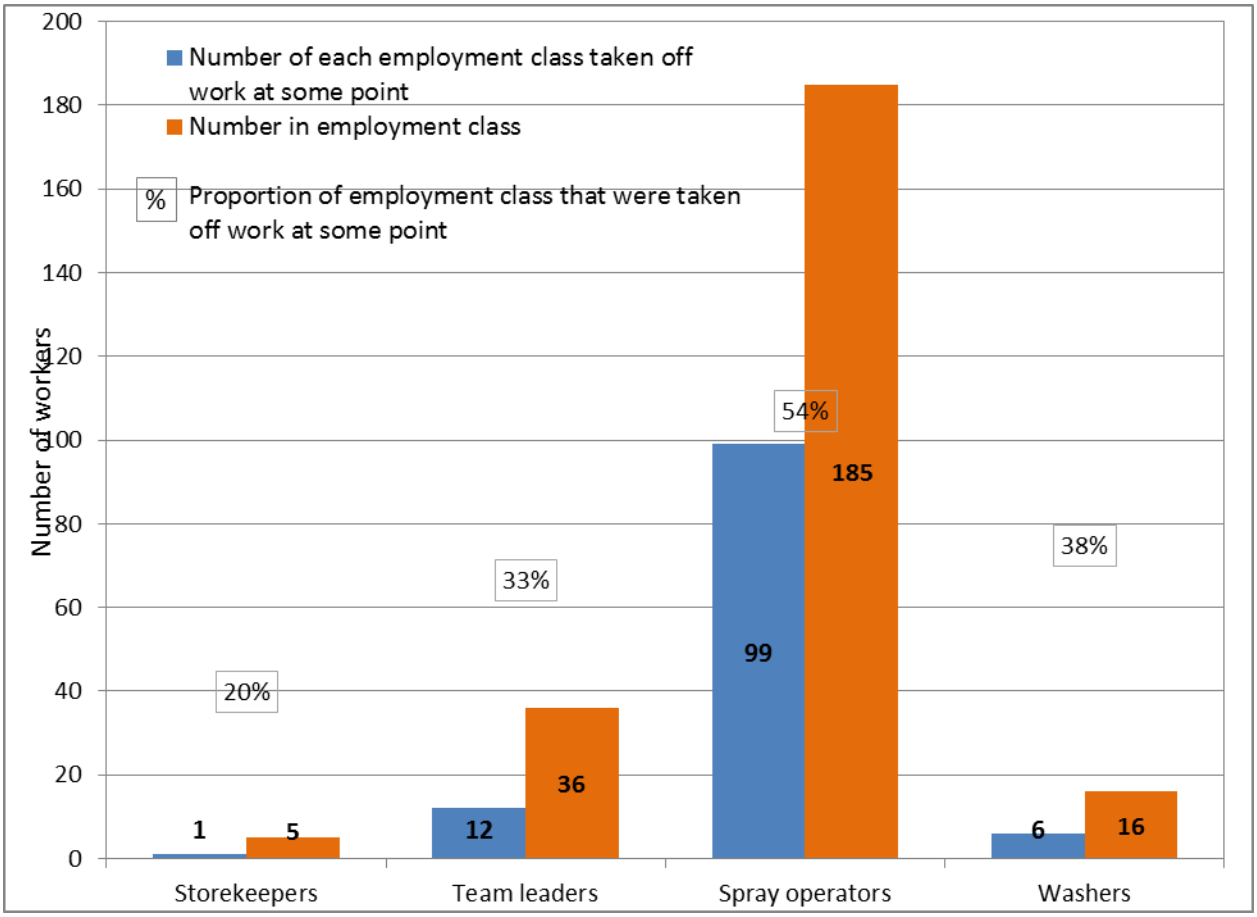
FIGURE 4. PROPORTION OF CASES WITH CHOLINESTERASE DEPRESSION BY SITE





Four classes of IRS workers were included in the biomonitoring testing pilot: SOPs, team leaders, washers, and storekeepers. In all, 118 of the 242 workers who participated in the pilot had to be removed from operations at some point during the campaign.[2] Figure 5 presents the number and proportion of workers in the different labor classes that were taken off their normal work schedule as a result of measured CD. One storekeeper (20 percent) at Kumbungu was removed from operations for PChE depression in the red category based on the results from Follow-up Two and her subsequent results indicated minor recovery. Among the 185 SOPs who participated in the pilot, 99 (54 percent) were at some point removed from operations.

FIGURE 5. NUMBER AND PROPORTION OF WORKERS IN LABOR CLASSES REMOVED FROM OPERATIONS



We contacted 199 participants after the end of the spray campaign to collect additional information that could help in explaining the observed trends in CD. Of the 199 participants, 16 (13 SOPs, 2 team leaders and 1 washer) indicated using pesticides within 3 months of the start of the IRS campaign. Four of these 16 had to be removed from operations at some point. Three SOPs also reported using pesticides on their farms during the IRS campaign. Only one SOP of the three had to be removed from operations for CD in the yellow category during follow-up two, but recovered enough by the retest.

[2] The list of workers was not the same each week as three workers left the campaign during the season for various reasons and three workers were hired mid-season to make up the numbers.

Based on the results of the post-spray interviews with the workers, the two districts that used only Hudson pumps (BYD and WMD) during the spray campaign had the lowest proportion of SOPs with CD during the campaign (Table 10). Both of these districts had less than 50 percent of the SOPs removed from operations. In addition, these two districts recorded the lowest average AChE and PChE changes for all workers over all 5 follow-up tests. KD, MMD and EMD all started with Goizper pumps but some of these were replaced by Hudson in the middle of the operation due to problems with the Goizper pumps. More problems with leakage and malfunctioning were reported with Goizper pumps and this may have a role for the higher number of CD from these sites.

TABLE 10. OBSERVED RELATIONSHIP BETWEEN SPRAY PUMP USED AND CD BY DISTRICT

	Average proportion of work days used		Proportion of workers with CD	Average AChE change	Average PChE change
	Goizper	Hudson			
BYD	0.00	1.00	0.46	0.56%	-7.16%
EMD	0.99	0.01	0.58	3.46%	-10.67%
KD	0.67	0.33	0.58	-0.70%	-12.72%
MMD	0.65	0.37	0.75	1.15%	-17.86%
WMD	0.00	1.00	0.24	1.90%	-6.31%

Exposure to the IRS chemical from a sprayed residence could have contributed to the measured CD of participants of the biomonitoring pilot. Of the 199 respondents, 183 indicated that their homes were sprayed, and 86 of these workers were removed from spray operations at some point as a result of CD. Of the 86 workers, 35 had their homes sprayed before the first instance of CD in the yellow or red category.

Table 11 presents some selected characteristics of the workers who had to be removed from spray operations at some point as a result of CD in the yellow or red category. In general, SOPs who were removed from operations used more pesticides a day on average and spent more time spraying with Goizper pumps. Age of the worker doesn't seem to have been a factor in the likelihood of being exposed but workers removed from operations seemed to be less experienced on average. With regards to gender, 66% of the workers removed from operations at some point were male (accounting for 51 percent of all male participants) and 34 percent were female (accounting for 45% of all female participants).

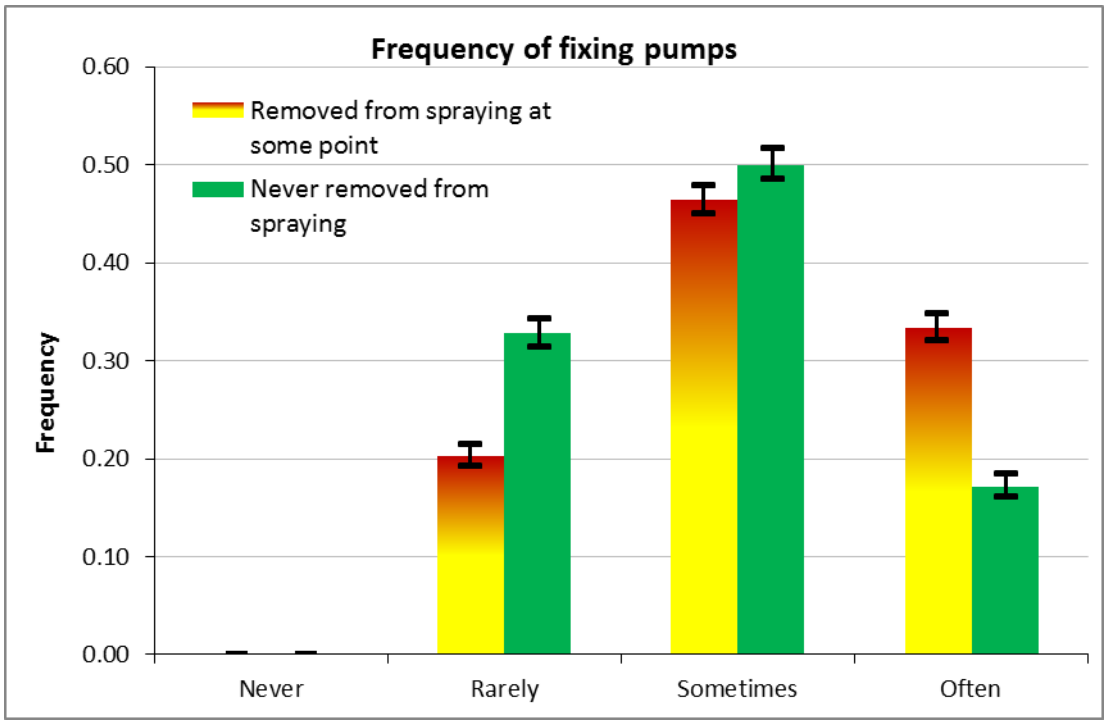
TABLE 11. SELECTED CHARACTERISTICS OF WORKERS REMOVED FROM OPERATIONS

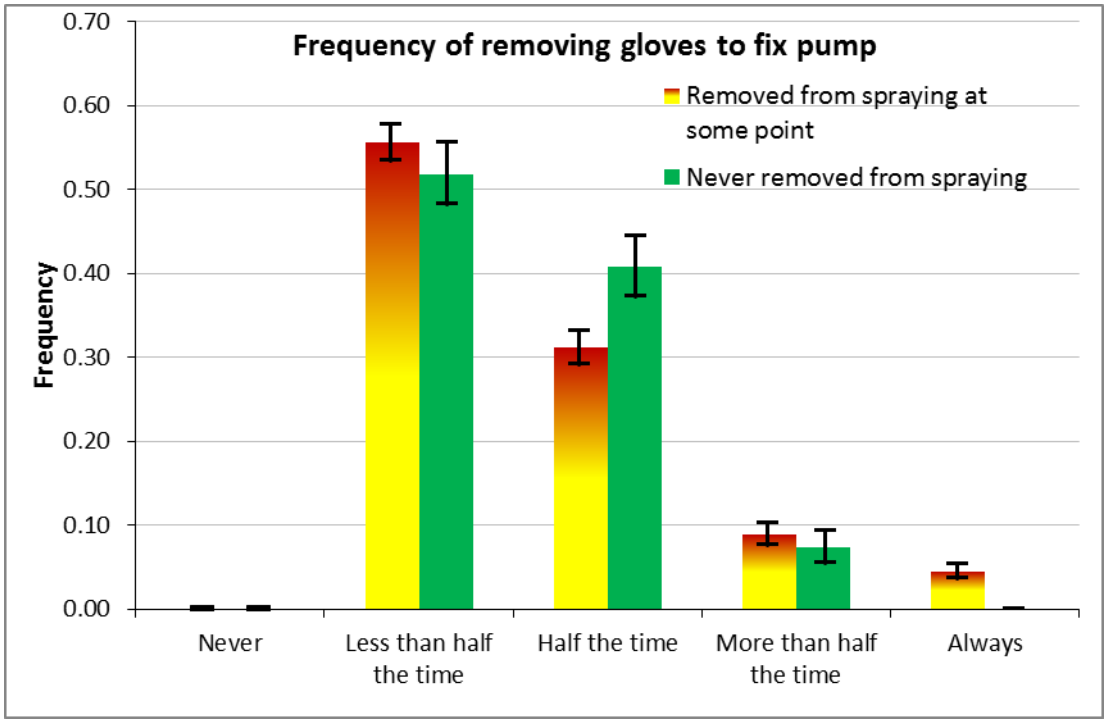
	Average number of bottles used/day of work	Average Age (years)	Average Experience (years)	Average proportion of Goizper days	Average proportion of Hudson days
Removed	3.8 (±0.2)	25.4 (±0.8)	1.6 (±0.2)	0.6 (±0.1)	0.4 (±0.1)
All Green	3.6 (±0.2)	25.5 (±0.9)	2.1 (±0.2)	0.4 (±0.1)	0.6 (±0.1)

Figure 6 presents a relationship between the frequency of SOPs having issue with the pump nozzles and being removed from operations as a result of CD. Among 144 SOPs who were contacted, 56 of the 113 who indicated having to fix their pumps often were removed from operations at some point. In addition, all those

who indicated that they always removed their gloves to fix the pump nozzles were at some point removed from operations as a result of CD.

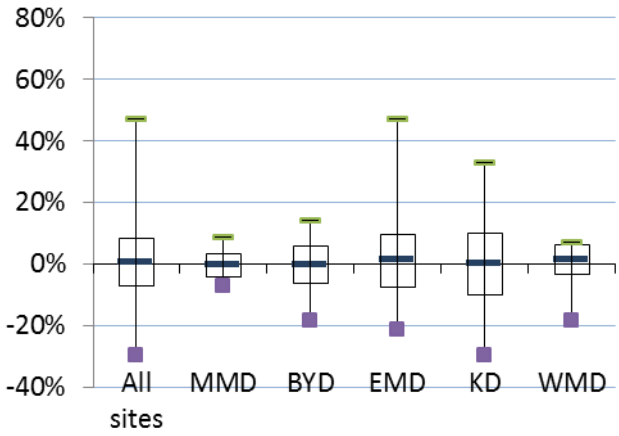
FIGURE 6. FREQUENCY OF SPRAY OPERATOR ISSUES WITH PUMPS



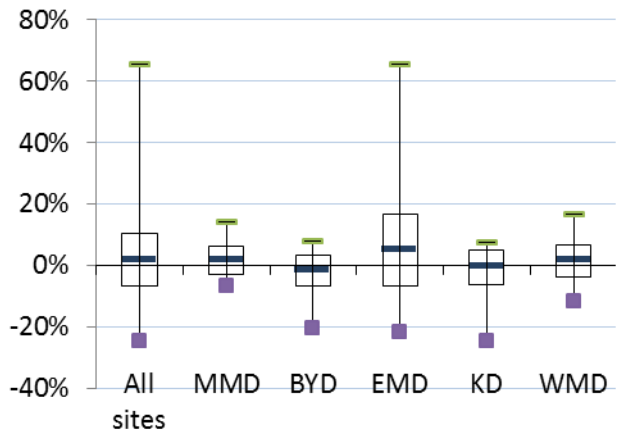


Figures 7 and 8 present the distribution of AChE and PChE changes for all sites for the five follow-up tests compared to the selected baselines. It should be noted that WMD completed all spray activities on time; therefore no follow-up five tests were conducted at that site. The ends of the lines correspond to the high and low values, the short blue line corresponds to the mean values, and the rectangular box shows one standard deviation from the mean for each site. In virtually all sites and for all follow up tests, the mean AChE change compared to the selected baselines was very close to 0%: in some cases the mean AChE change was greater than 0 percent. In addition, the recorded AChE depression was greater than 30 percent in only one case (in EMD). However, the means of the PChE changes compared to the baselines were less than 0 percent for most sites and for most follow-up tests. The ranges of PChE change compared to the baseline was quite wide during follow-up one and follow-up two, but became more narrow during the last three follow-up tests.

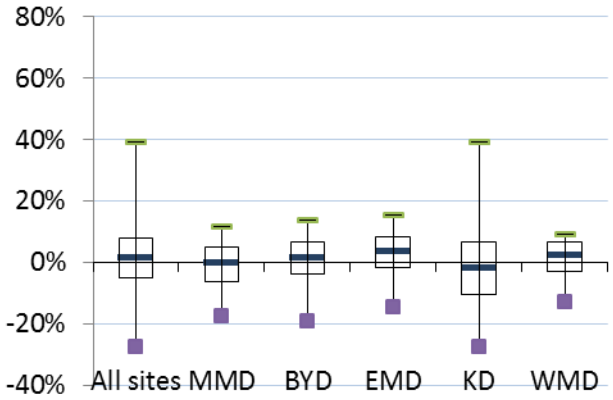
FIGURE 7. DISTRIBUTION OF ACHE DEPRESSION BY SITE FOR ALL FOLLOW-UP TESTS



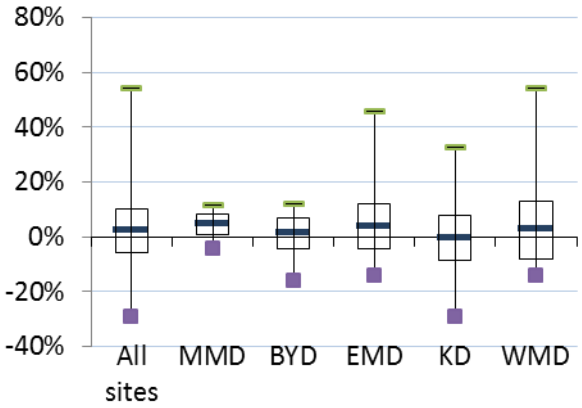
Follow-up 1



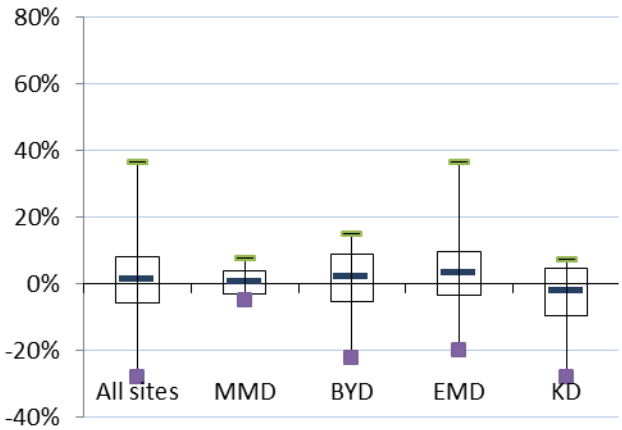
Follow-up 2



Follow-up 3

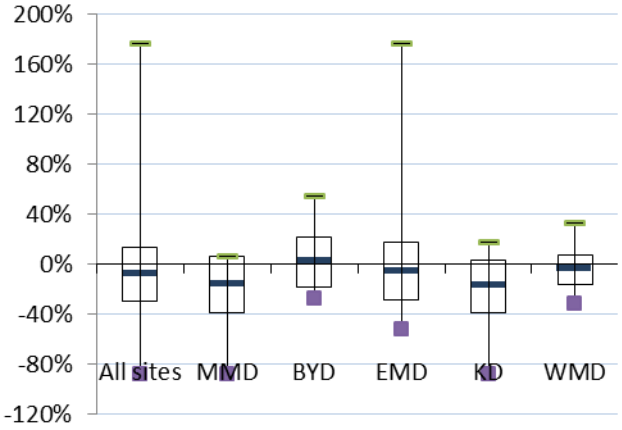


Follow-up 4

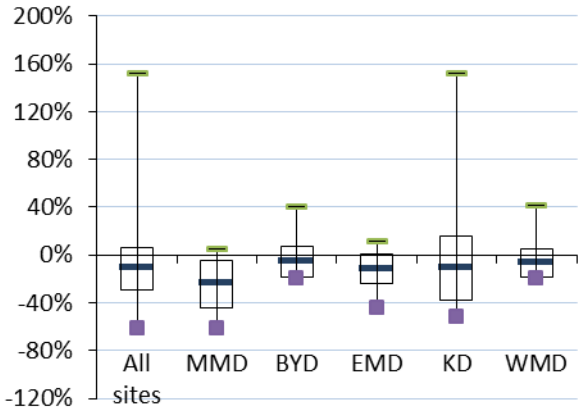


Follow-up 5

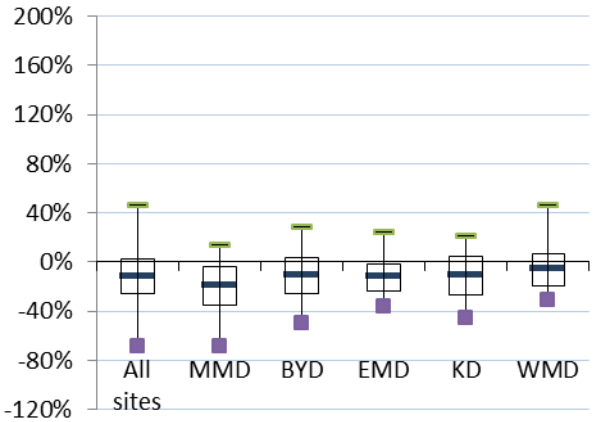
FIGURE 8. DISTRIBUTION OF PCHE DEPRESSION BY SITE FOR ALL FOLLOW-UP TESTS



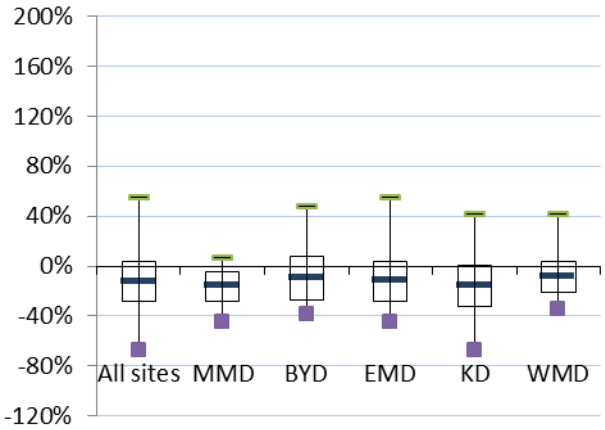
Follow-up 1



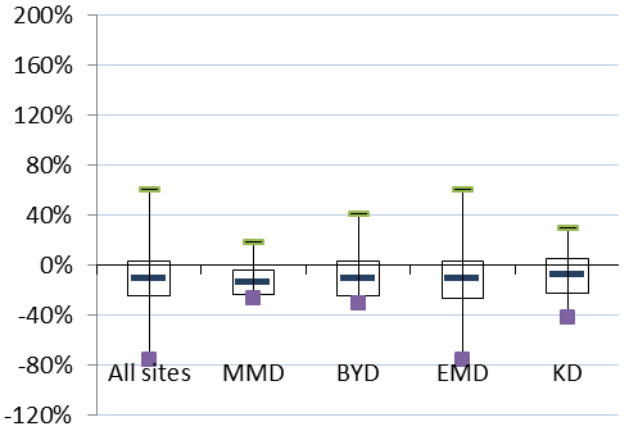
Follow-up 2



Follow-up 3



Follow-up 4



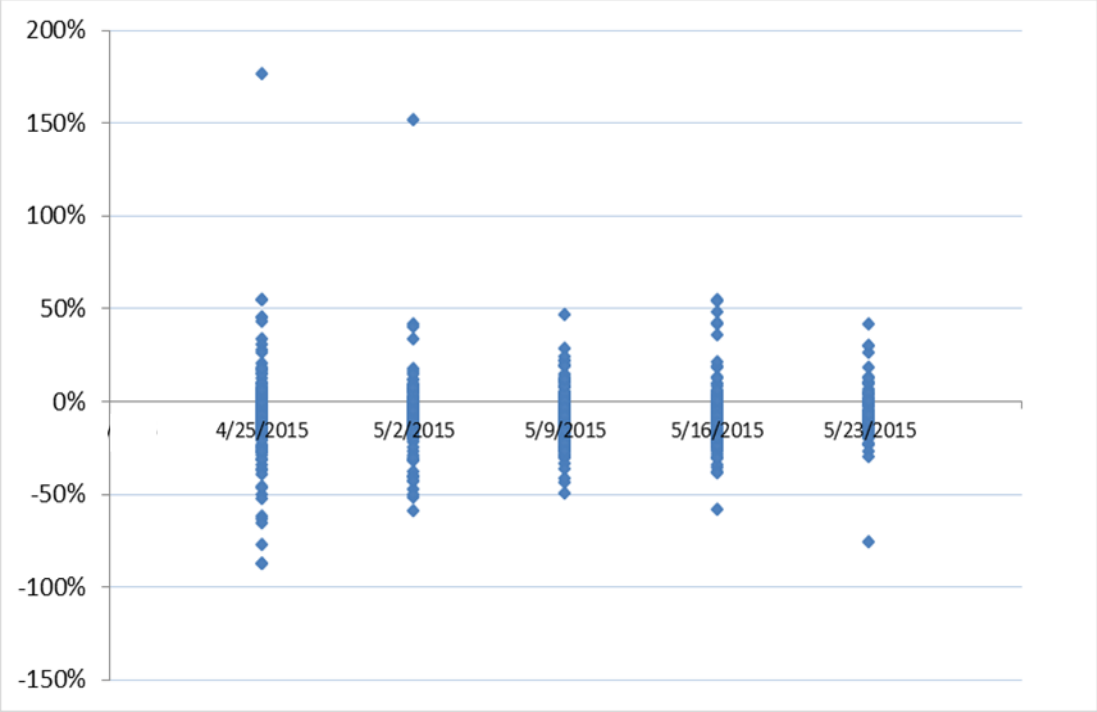
Follow-up 5

The top panel of Figure 9 presents a scatter plot of all PChE changes compared to the baseline. The PChE changes are concentrated below the 0 percent (no change) line for all follow-up tests. The histogram in Figure 11 shows that the majority of the PChE changes compared to the baseline were less than -10 percent (i.e., more than 10 percent depression). The histogram for the AChE changes is to the right of the histogram for PChE changes.

The lower panel of Figure 9 presents a comparison between the PChE for the two groups of workers – those with pre-exposure and those with post-exposure baselines. In the graph, a blue dot indicates a PChE change for a worker in the group of workers with post-exposure baselines and an orange "x" indicates those of the 50 workers who were held back from spraying until a pre-exposure baseline was obtained. The PChE changes compared to the baseline for the 50 workers with pre-exposure baselines were generally more positive than those for the other workers with their post-exposure baselines taken into account. On average, for the five follow-up tests, the median for PChE changes for the 50 workers with a pre-exposure baseline was more positive than the median for the workers with a post-exposure baseline.

Figure 10 presents similar graphs for AChE changes compared to the baseline. The upper panel presents the AChE changes from the baseline for all workers over the 5 follow up tests. Unlike for PChE, the majority of AChE changes were greater than 0 percent. This is also evident from the histogram presented in Figure 11. The lower panel of Figure 10 presents separate scatter plot that separates the AChE changes for the workers with post-exposure baselines and workers with pre-exposure baselines. In this case, although the AChE depression for the workers with pre-exposure baselines never indicated CD of the yellow or red category, the median of these values was less than the median of the AChE changes for the workers with post-exposure baselines.

FIGURE 9. DETAILED DISTRIBUTION OF PCHE CHANGES FOR ALL FOLLOW-UPS



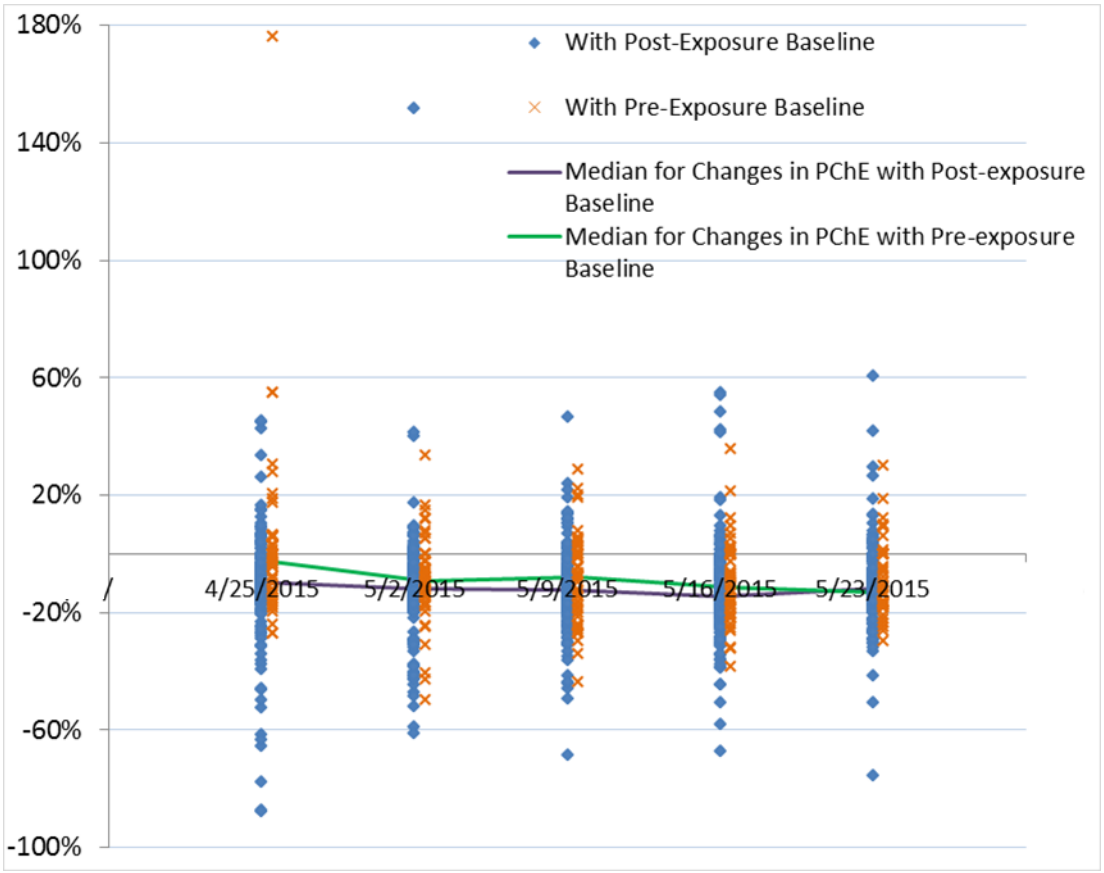
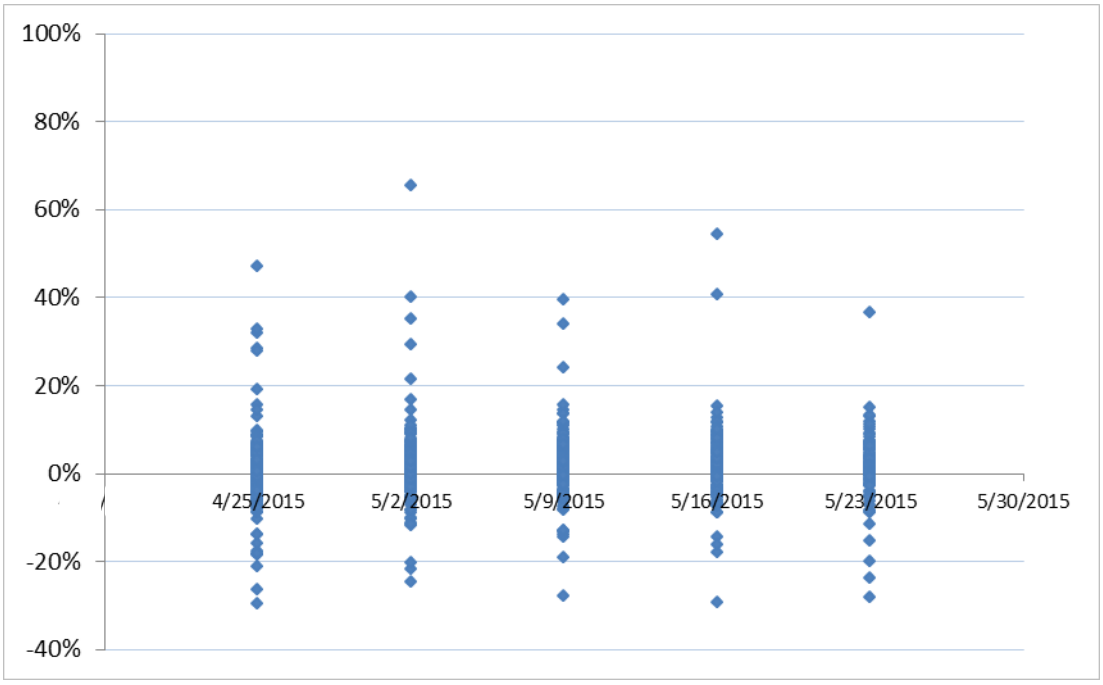

180%
140%
100%
60%
20%
-20%
-60%
-100%
With Post-Exposure Baseline
With Pre-Exposure Baseline
Median for Changes in PChE with Post-exposure Baseline
Median for Changes in PChE with Pre-exposure Baseline
4/25/2015
5/2/2015
5/9/2015
5/16/2015
5/23/2015

FIGURE 10. DETAILED DISTRIBUTION OF ACHE CHANGES FOR ALL FOLLOW-UPS



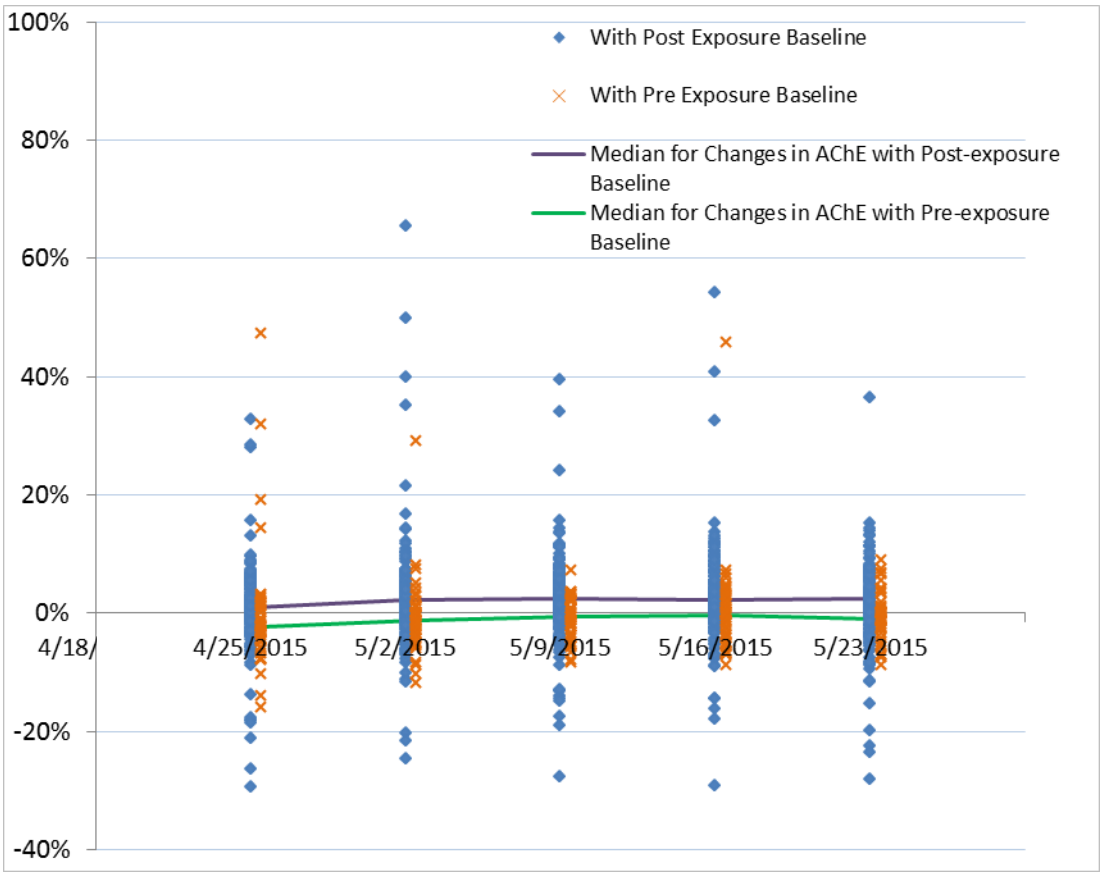
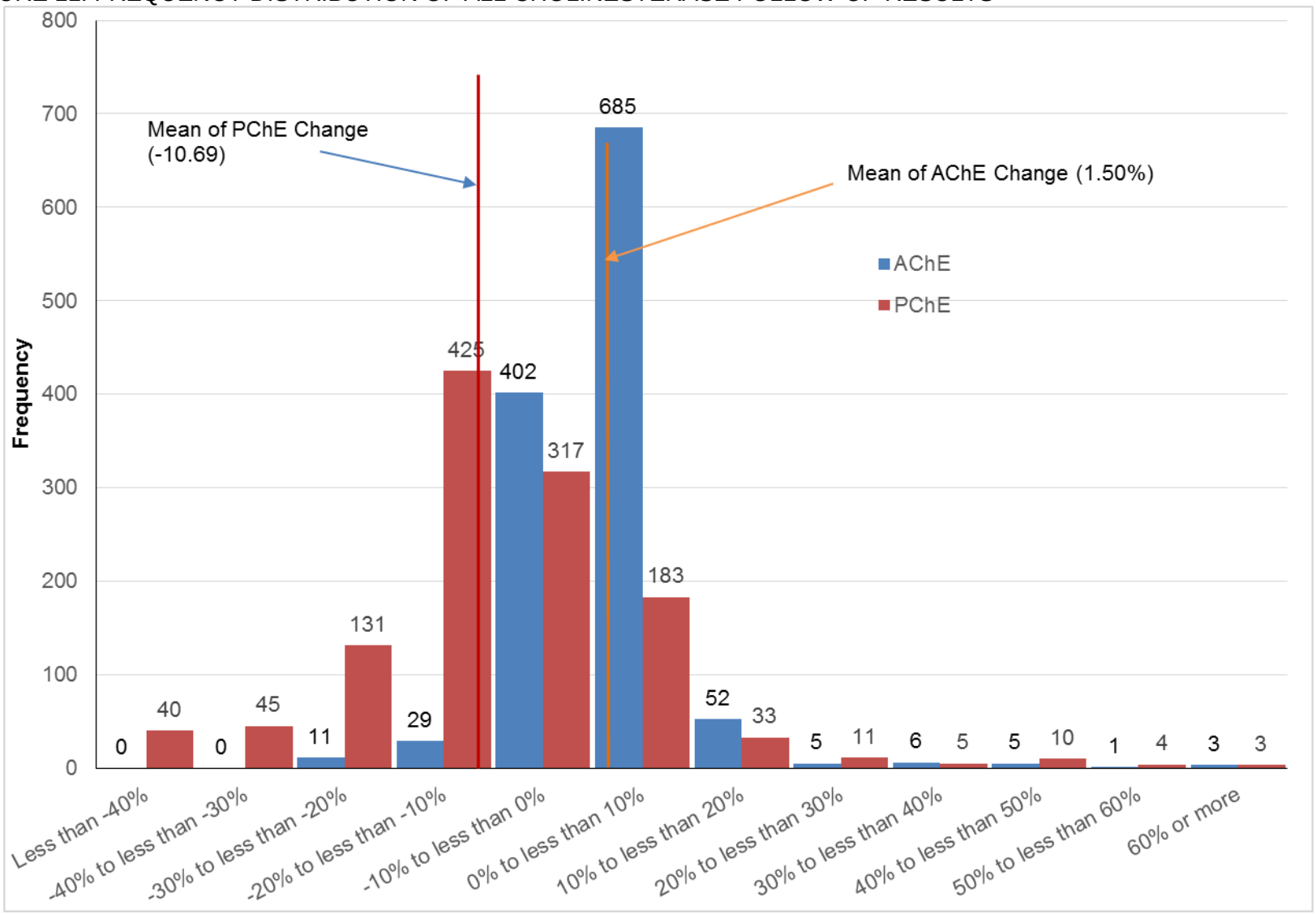


FIGURE 11. FREQUENCY DISTRIBUTION OF ALL CHOLINESTERASE FOLLOW-UP RESULTS



We explored the impact of adjusting for the potentially inaccurate baselines obtained with the degraded reagents by using a post-exposure baseline for part of the participants. In order to do so, we compared two approaches taken. One approach involved obtaining the baseline as either an average of a pre-exposure test with old reagents and a one-week post-exposure test, or the higher of the two tests. The other approach involved using the lower of the two tests as the baseline.

Figure 12 presents the distribution of the AChE and PChE changes compared to the baseline for all workers who had a one-week post-exposure test included in the baseline measure. Similar to the distribution for all workers, the PChE histogram (in red) lies largely to the left of the AChE histogram (in blue). The majority of the PChE changes from the baseline show depression of 10 percent or more. When the lower of the two baseline values – one post-exposure baseline and one baseline using the old test kits – is used as the reference baseline (see Figure 13), the histogram for PChE changes was still centered to the left of the histogram for AChE changes. The Figure 13 excludes the 50 SOPs with only pre-exposure baselines. However, the majority of PChE changes were -10 percent or more. Fewer cases of CD (of both the red and yellow category) would have been identified over the five follow-up tests. Among the 50 workers with pre-exposure baselines, the distribution of PChE changes from the baseline (see Figure 14) was also to the left of the distribution of AChE changes. The median of PChE changes for the 50 workers with pre-exposure baselines was -8.66 percent – higher than the median for the workers with post-exposure baselines (-11.76 percent) – and the median for AChE changes for the 50 workers was -1.16 percent – lower than the median for the workers with post-exposure baselines (1.98 percent).

FIGURE 12. FREQUENCY DISTRIBUTION OF ACHE AND PCHE CHANGES FROM BASELINE FOR ONLY WORKERS WITH POST-EXPOSURE BASELINES

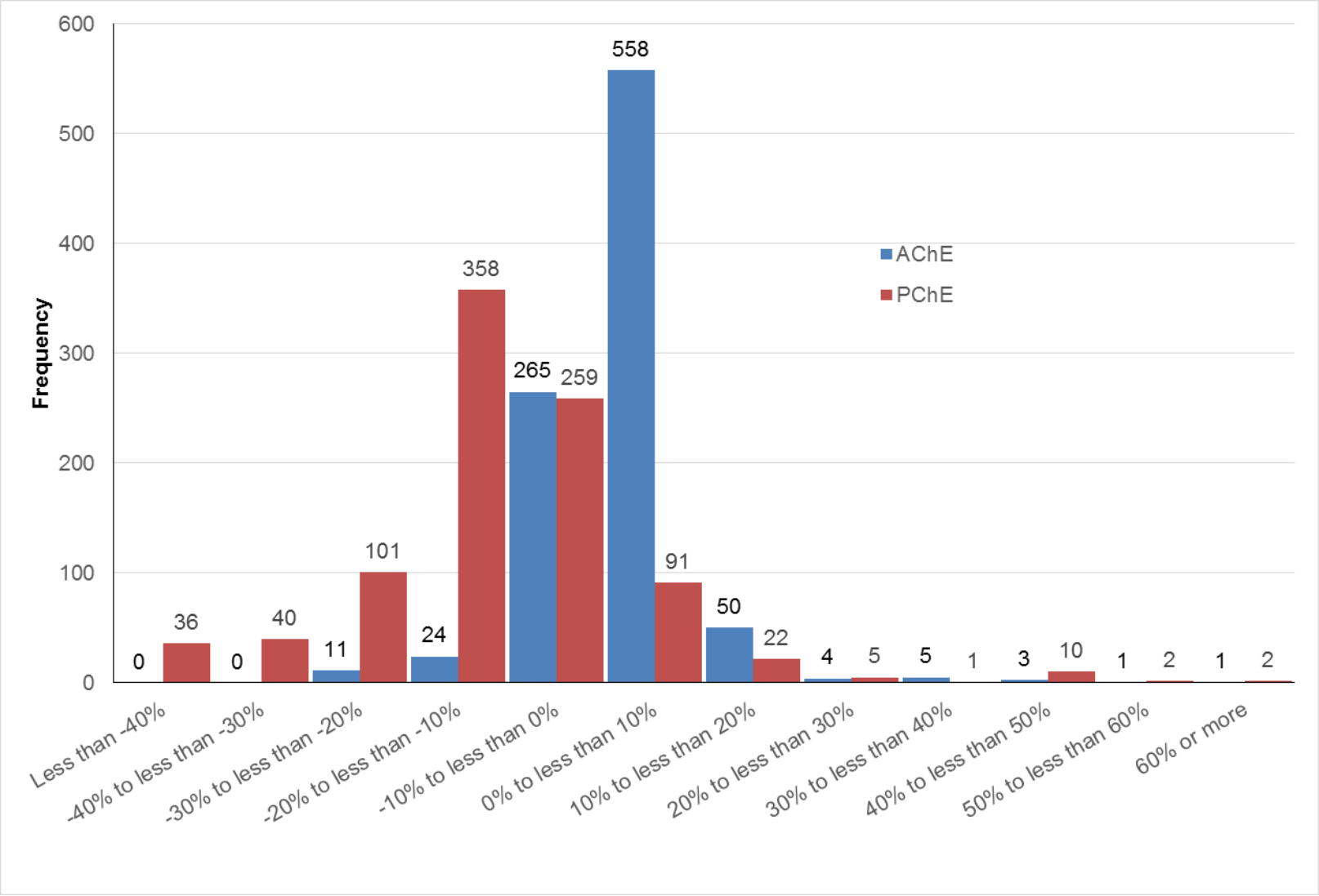


FIGURE 13. FREQUENCY DISTRIBUTION OF ACHE AND PCHE CHANGES FROM BASELINE FOR ONLY WORKERS WITH POST-EXPOSURE BASELINES, USING MINIMUM OF TWO BASELINES

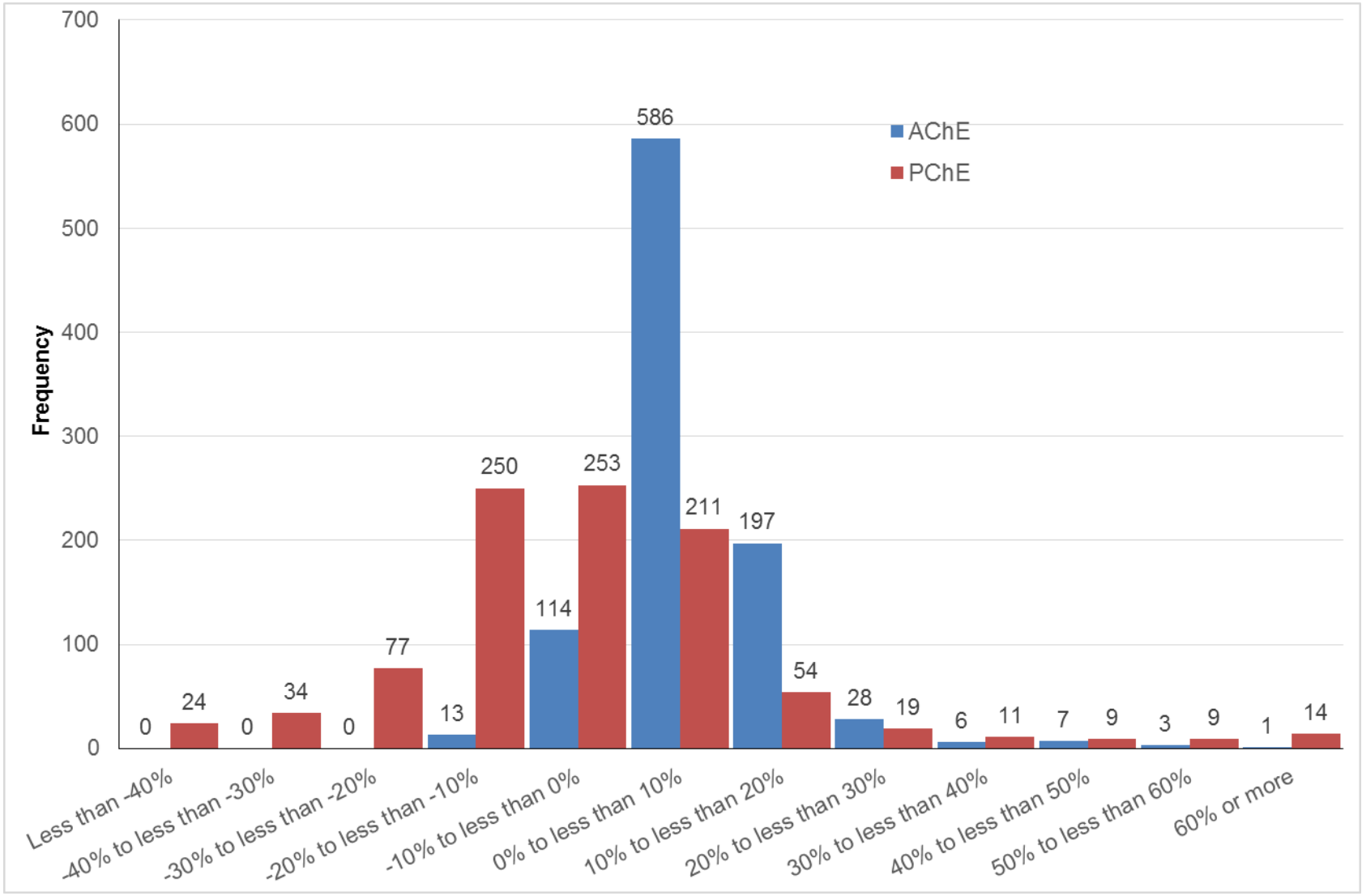


FIGURE 14. FREQUENCY DISTRIBUTION OF ACHE AND PCHE CHANGES FROM BASELINE FOR ONLY WORKERS WITH PRE-EXPOSURE BASELINES

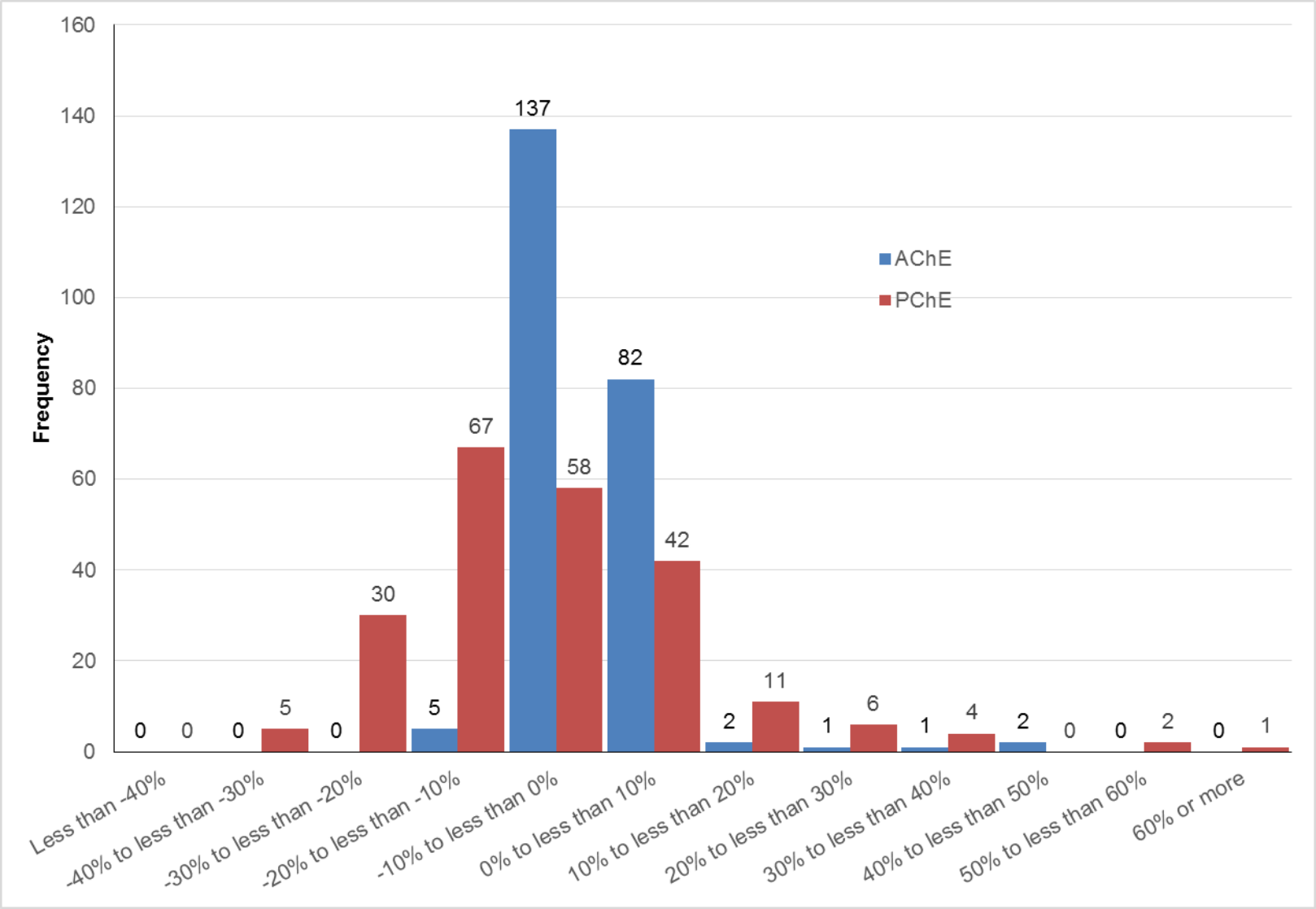
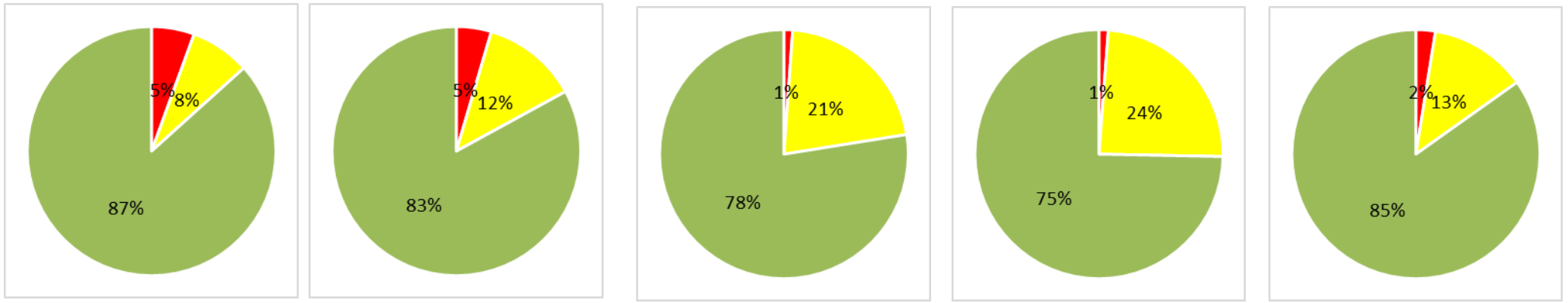


Figure 15 examines the differences between the proportion of men and women with CD over the five weekly follow-up tests. Results indicate that there didn't seem to be any obvious differences between men and women in terms of the proportion of participants with CD.

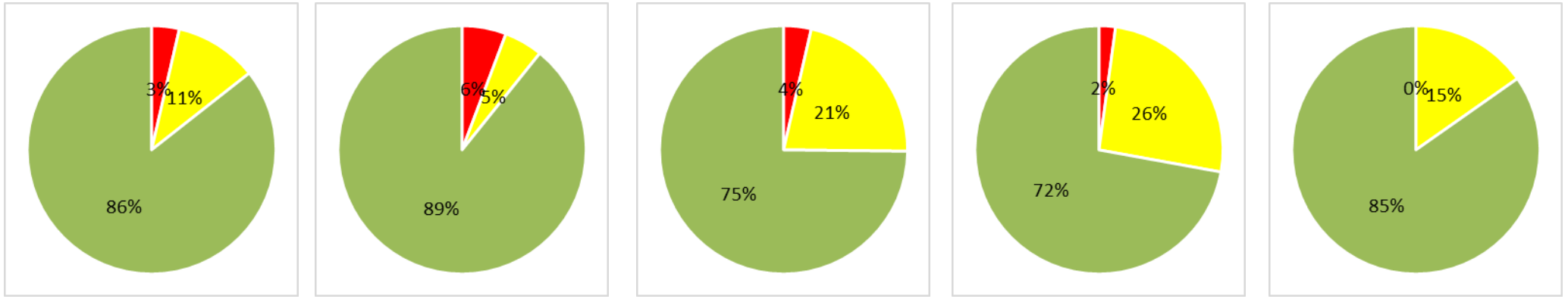
FIGURE 15. DIFFERENCE BETWEEN THE PROPORTION OF MALES AND FEMALES WITH CD, FIVE TEST SITES

Follow-up 1 **Follow-up 2** **Follow-up 3** **Follow-up 4** **Follow-up 5**

Women



Men



Feasibility:

Implementation of this pilot biomonitoring program was challenging and labor intensive. The most significant challenges faced included:

- **The reagents used in the test kits are sensitive to extreme heat and degrade when the temperature reaches 30 degrees Celsius**. The temperature at the test sites was routinely hotter than 30 degrees Celsius, as are many IRS operational sites across sub-Saharan Africa. The original test kits brought to Ghana in 2014 were not stored at optimum conditions given power shortages and shortages of refrigerators in remote areas of Ghana. Therefore, the baseline data collected using these kits were not reliable and had to be partially discarded as invalid while new test kits were procured and a new methodology was developed to account for this baseline testing error. In addition, to ensure that the newly procured test kits did not degrade, the project had to procure air conditioners, generators for backup power, and refrigerators, increasing the cost of the pilot.
- **The labor involved in implementing the biomonitoring pilot impacted the project's ability to conduct IRS**. The spray operation had to be extended by three days and additional workers needed to be trained in order to compensate for the workers removed from IRS operations. In addition, because IRS supervisors had to attend all tests at all sites for biomonitoring, they were diverted during portions of the IRS season from managing tasks related to the spray campaign. Finally, the Chief of Party diverted more than 25 percent of his time during the spray campaign to the biomonitoring pilot.
- **In several instances, the lab technicians could not conduct the tests because they were needed in their regular positions at the health facilities**. Dedicated lab technicians were not feasible given costs and lack of sustainability, therefore the only option was for the project supervisors to perform the tests (which further diverted their attention from supervising IRS operations).
- **Ensuring adequate test kits for the pilot as the supplier had to produce them on demand**.

COST

The overall cost of the biomonitoring program was $215,960, with the bulk of the expenses representing recurring costs. Costs incurred by the AIRS Ghana program ($81,200) were predominantly comprised of the programmatic expenses for training and supplies. The remaining costs ($134,760) were incurred by the Global Environmental Management Support Project (GEMS) and supported the design the original protocol, training of workers, monitoring of the implementation, and contributing to the analysis of the data.

The cost to compensate the workers temporarily removed from their original jobs or from the campaign due to identified CD risk, was $6,722 and covered their original daily wages and meals. The cost for the three-day period within the total of five–day extension of the spray campaign was $9,400, or 11 percent of the total biomonitoring cost.

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ANNEX O: COMPILED FEEDBACK FROM THE PUBLIC REVIEW

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
1. I was pleased to note the integration of material regarding the nets being used for fishing. (*USAID*)	n/a
2. As I was looking through this PEA, I noticed that there could be a greater emphasis on preventative and non-chemical measures, in addition to the chemical approaches. As you know, WHO provides a summarized resource regarding vector tools for more effective control. These preventative and non-chemical methods can address the following strategic areas: environmental modification, environmental manipulation, human settlement siting and management, and natural predators for larval. These non-chemical management strategies are simply part and parcel of local approaches for vector management. These issues could be placed in their own section or sub-section within the PEA or just a part of the suite of approaches. It may be worth considering developing a tool - e.g. a checklist for partners of both chemical and non-chemical strategies - to accompany this information. (*USAID*)	USAID acknowledges that these non-chemical management strategies can indeed be part and parcel to local approaches for vector management. However, because the vast majority of USAID malaria resources are via PMI, and PMI prioritizes support for proven life-saving malaria control and prevention strategies that can be taken to scale, environmental modification and manipulation, human settlement siting and management, and natural predators for larval are not assessed in this PEA.
3. "Cancer risks are not shown graphically because only two active ingredients (permethrin and diflubenzuron) were considered as possible human carcinogens." The document states that diflubenzuron is a probably carcinogen and human exposure assessments have been presented with the consideration that diflubenzuron is a carcinogen. To clarify diflubenzuron is not classified as a carcinogen by any global regulatory authority. The EPA classification of diflubenzuron is group E, no evidence of carcinogenicity. The EU classification does not classify diflubenzuron for carcinogenicity mutagenicity, toxicity or reproduction. Please amend this text and remove reference to diflubenzuron. (*Manufacturer*)	*Original response to reviewer*: The text referenced from p. 53 will be revised to clarify that 4-chlorophenylurea (CPU), a water degradation product of diflubenzuron, is the specific chemical for which carcinogenic risk is evaluated. Although EPA has determined that there is no evidence of carcinogenicity for diflubenzuron (Group E), EPA considers CPU a probable human carcinogen and provides a cancer slope factor for CPU in Table 1 of the 2014 Pesticide Tolerances rule for diflubenzuron and evaluates cancer risk related to dietary exposure from drinking water. Cancer risk calculations will be limited to evaluation of carcinogenicity in the residential scenario, where human exposure is related to drinking water that may contain the degradation product CPU. Annex C tables related to worker cancer risk will be removed. The product/a.i. will be labeled "Diflubenzuron; 4- chlorophenylurea metabolite" in Annex C tables. *Reviewer's dissent*: Thank you for your response
4. Table 4-3 (page 63), Table C2-3b, Table C1-3b, table C1-3d, Table C2-3b, Table C2-3b: Diflubenzuron is not a possible human carcinogen therefore should not be considered in a cancer risk exposure scenario. (*Manufacturer*)	
5. Table Diflubenzuron (35367-38-5) – growth regulator: 4-chlorophenylurea is confirm as having the same toxicity profile as parent and therefore should not	

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
be considered as a carcinogen (*Manufacturer*)	and the opportunity to review the proposed amended text. We welcome your amendment to the text to accurately reflect that diflubenzuron is not classified as a carcinogen and also addressing the requirement to perform worker exposure for the low level impurity PCA. However as stated previously there is no requirement to consider CPU as a carcinogen. I believe the misunderstanding is derived from the EPA statement in in https://www.gpo.gov/fdsys/pkg/FR-2014-01-31/pdf/2014-02064.pdf where the EPA were considering the *structural analysis* of CPU and similarity to monuron, *a compound producing tumors in rats*. Based on the structural analysis and not data the EPA hypothesized that CPU was a possible human carcinogen. However in the 2014 document and the more recent 2016 EPA review (https://www.federalregister.gov/documents/2016/02/12/2016-02816/diflubenzuron-pesticide-tolerances) the EPA also considered the dose relationship and stated that CPU should be considered **in the non-carcinogen risk**. As stipulated in my response on Sept 8th 4-chlorophenylurea (CPU) is confirm as having the same toxicity profile as the parent, diflubenzuron, and therefore should not be considered as a carcinogen. CPU is considered as a major metabolite of diflubenzuron in rats as found in the urine, faeces and eventually in the bile in peer reviewed and regulatory accepted rat metabolism studies. There is also a regulatory acceptable comparative metabolism study which confirm that the metabolism of diflubenzuron in rats is equivalent to human metabolism. The possible toxicity of CPU and consideration of CPU as a possible human carcinogen can therefore be considered to be covered by the diflubenzuron data package. i.e the diflubenzuron metabolism study confirms that CPU is a major metabolite of diflubenzuron therefore CPU has been adequately tested in the carcinogenicity studies of diflubenzuron and thus confirmed not to be a carcinogen. To conclude CPU is not a carcinogen and there is no requirement to perform a carcinogenic risk evaluation for this metabolite and by default there is no requirement to perform a carcinogenic risk for diflubenzuron. This is confirmed by Regulation (EC) No 396/2005, the residue definition for Diflubenzuron is the sum of Diflubenzuron and

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
	CPU (4 –chlorophenylurea) expressed as Diflubenzuron. Therefore the toxicity of CPU is addressed by the parent toxicity package. As stipulated above the EPA consideration of CPU as a probable carcinogen is due to the structural comparison of CPU and monuron. There is clear scientific evidence that CPU is not a carcinogen and in addition the IACR concluded that monuron is not classifiable as to its carcinogenicity to humans (Group 3)" (https://monographs.iarc.fr/ENG/Monographs/vol53/mono53-19.pdf). The EPA have also concluded that CPU should be considered in the non-carcinogenic risk. There is available robust scientific data to support that CPU is not a possible human carcinogen therefore we respectfully request that the consideration of the cancer risk for CPU, a water degradation product of diflubenzuron, is not scientifically warranted and is a misrepresentation of scientific data. *Final response to reviewer*: Our collective review of your concerns suggests that there are two primary arguments that you have presented regarding the potential carcinogenicity of CPU and the calculation of drinking water cancer risk for CPU in the Programmatic Environmental Assessment (PEA). The first argument is that CPU should be addressed for noncarcinogenic effects, and by implication not for carcinogenic effects. The second argument is that the preponderance of scientific evidence indicates that CPU is not carcinogenic and that evaluation of potential carcinogenic effects is therefore inappropriate. With respect to the first argument, we have reviewed EPA's 2014 and 2016 Pesticide Tolerances final rules to determine if EPA has stated that evaluation of the non-carcinogenic effects of diflubenzuron and its metabolites are protective of potential carcinogenic effects. In other words, can the potential carcinogenic effects of CPU be ignored if noncancer effects are evaluated and found to be below a threshold of concern? We have found no statement to that effect in either the 2014 or 2016 Pesticide Tolerances final rules. The inclusion of a carcinogenic effects benchmark for CPU in Table 1 of EPA 2014 (summary of toxicological doses and endpoints for dietary human health risk assessments), and the

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
	evaluation of drinking water cancer risks for CPU in the 2014 and 2016 final rules, indicates that EPA supports evaluation of cancer risk for CPU. With regard to the contention that scientific evidence indicates that CPU is not carcinogenic, it is important to recognize that USAID is not conducting an independent evaluation of the toxicology of diflubenzuron and its metabolites. Instead, USAID applies the current toxicological benchmarks recommended by EPA, relying primarily on chemical risk assessments supporting pesticide registration and reregistration eligibility decisions. As such, we note that CPU is addressed with respect to both non-carcinogenic effects (Table 2; potential effects of the metabolite CPU are included in the non-cancer assessment of diflubenzuron) and carcinogenic risks (Table 1; potential effects are based on the structural analog monuron). USAID recognizes that other agencies and organizations may reach different conclusions than EPA regarding the evaluation of CPU carcinogenicity.
6. Table Diflubenzuron (35367-38-5) – growth regulator: 4 –chloroaniline (PCA) is a relevant impurity in technical diflubenzuron at < 30ppm. Toxicity of the impurity is addressed by the toxicity of the parent, diflubenzuron. PCA is a transient, non-isolatable metabolite in humans and is confirmed not to be formed during metabolism in plants and is not found above the LOQ in plant residue studies. There is therefore no evidence to support that PCA is a plant metabolite and this statement should be retracted. (*Manufacturer*)	Risk assessment calculations were not performed for 4–chloroaniline (PCA). To avoid confusion this row will be removed from the diflubenzuron table in Annex D-3.
7. There is no requirement to perform worker exposure assessments for PCA as the level of PCA as an impurity has been adequately tested in the toxicity studies of the parent and confirmed to be addressed. (*Manufacturer*)	
8. p. 18: Under IRS need to make it clear that the numbers e.g. Pirimiphos-methyl Capsule Suspension (CS) 1000 refer to the application rate in mg/m2. This is potentially misleading. (*Manufacturer*)	A footnote has been added to address this.
9. p. 18 and 23: Clothianidin (SumiShield) is a WG not a WP. (*Manufacturer*)	The text will be revised and the assessment calculations revised to evaluate as WG. The impact on results was minor since worker risks were already small and this change reduced them further.
10. p. 27: The 36/32 figures are incorrect, at 40 gsm Olyset Duo contains 800 mg/m2 Permethrin and	New risk assessment results have been developed using the values (800 and 400

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
400 mg/m2 Pyriproxyfen. This will affect all the subsequent risk assessment calculations. Note also that the spelling of pyriproxyfen is incorrect. (*Manufacturer*)	mg/m2), cited here.
11. p. 27: Note also that the spelling of pyriproxyfen is incorrect. (*Manufacturer*)	The spelling of pyriproxyfen has been corrected.
12. p. 61: States that the permethrin content of Olyset Duo which is 36 mg/m2; this is incorrect (see above). (*Manufacturer*)	The text interpreting the relative results for Olyset Duo and Olyset Plus has been revised.
13. p. 15: States WHOPES approved – no product is approved by WHOPES they are `recommended` please correct. (*Manufacturer*)	The text has been revised.
14. p. 23: There is a serious error here in dose rates. Clothianidin WG is reported as being 300 g ai/m2 but is 300 mg ai/m2!! The dose rate for Chlorfenapyr is also incorrect. You are mixing mg/m2 with g/m2. Please review and correct. (*Manufacturer*)	These were typographical errors and the table has been corrected. The correct values/units were used in calculations.
15. p. 26: Polypropylene nets are not cost effective and are no longer available. (*Manufacturer*)	The text has been revised accordingly.
16. p. 5: Spelling mistake in table – Olyset Plus – Piperonyl oxide should be butoxide. (*Manufacturer*)	This has been corrected in Table 4-2
17. p. 76: Please also note that the cancer risk for permethrin-treated hammocks is above the target cancer risk of 1 in 10,000 for dermal exposure in adults during sleeping. (*Manufacturer*)	This appears to be reported correctly and acknowledged in the text.
18. p. 18, line 27 and p.27: "Alpha-cypermethrin and chlorofenapyr on polyethylene" This must read alpha-cypermethrin and chlorfenapyr coated on polyester (*Manufacturer*)	The text was revised accordingly.
19. p. 23: The target dose of chlorfenapyr is 0.25 g/m2 (*Manufacturer*)	We have updated the target dose to 0.25 g/m^2 as suggested, and rerun all risk assessment calculations based on this value.
20. p. 23: The target dose of alpha-cypermethrin is 0.02 – 0.03 g/m2 (*Manufacturer*)	The values were a typographical error and have been corrected. A value of 0.025 g/m2 was used in the risk assessment calculations.
21. pgs. 23 and 27 (note at the end says "The USEPA status for all active ingredients listed above is "active" except for alpha cypermethrin, bendiocarb, and DDT (which have a "cancelled" status)". Alpha is still registered by USEPAFASTAC Technical (=alphacypermethrin) registered under EPA Number 7969-299 on Jan 24 2013 (*Manufacturer*)	The text will be revised (the footnote was a leftover from the previous PEA, when alpha cypermethrin was inactive).
22. p. 33 and 43, last para: Industry should	As stated on p. 33 of the report, the purpose of

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
advocate against the so-called lax scenario for workers (no PPE, mentioned on pp. 33 and 43). This goes against all label recommendations, against WHO guidelines for use recommendation and against the overall idea that the products are applied by trained professionals (at least that is my understanding for IRS products and would also be my assumption for larvicides). (*Manufacturer*)	evaluating the "lax scenario" is to provide information for risk managers related to the need to develop mitigation strategies that address variability in safety compliance. This information is a supplement to risk calculations that assume compliance with an appropriate PPE program.
23. p. 59, para on Interceptor G2: Risk assessment for Interceptor G2, page 59: "Given the different mechanisms of action, the two insecticides in this product were considered to be additive, rather than synergistic, with regard to human health risk. Because both insecticides can induce neurological effects (albeit by different mechanisms) treating them as additive is reasonably conservative approach." BASF's toxicologists are of a different opinion and consider that since the two substances act independently, a combined risk assessment addressing potential combined is not required (see attached statement). (*Manufacturer*)	The EPA chronic exposure toxicity benchmarks (see Annex D3) for chlofenapyr and alpha-cypermethrin are both related to observations of neurotoxic effects in animal models. Summing of potential noncancer health effects to calculate a hazard index for these chemicals is therefore considered appropriate.
24. p. 213, Annex F3: The target dose for chlorfenapyr should read 250 mg/m2 (*Manufacturer*)	The risk assessment calculations will be updated using the correct value of 250 mg/m2 cited by BASF. The value has been corrected in Annex F3.
25. p. 213, Annex F3: A default dermal absorption of 10% is assumed in the calculations for all active ingredients as listed in Annex F3, which is in contradiction with Annex D3, where for chlorfenapyr a dermal absorption of 5% is recommended (*Manufacturer*)	The risk assessment calculations will be updated using the chemical-specific dermal absorption value of 5% in lieu of the default value of 10%.
26. The document is excellent, in all that it touches on, and the level of details for IRS/LLIN and Larvicide is really good. However, we are very concerned that the document misses out, without rational, some key tools for prevention that are already supported by WHO for use in emergency contexts, and that this will severely limit USAIDs support for effective malaria control in emergency settings, as OFDA depend also upon this document to guide what they will fund. Failure to include some tools for emergency settings, would reduce capacity to save lives and reduce suffering for many millions of victims of emergency settings (conflict and natural disasters), so we ask for your full consideration of the comments below please. • P. 19, line 11: Why is there no inclusion of insecticide treated plastic sheeting (ITPS) or blankets? These are essential malaria commodities for use in emergency settings, and their use is supported by	Given the PEA is most commonly used to guide USAID/Global Health malaria programming, and USAID funds for malaria within Global Health are distinct from those within OFDA, this revision of the PEA will not be revised to include IPTS or blankets. That said, USAID acknowledges the validity of the reviewer's comment, and there may be a growing demand for these types of interventions in emergency settings. Therefore, the next PEA revision (next year) will include these emergency control measures. In the meantime, if USAID is to support these measures (likely via OFDA), they would be subject to the environmental compliance procedures of 22 CFR 216 (e.g., development of an IEE or SEA, monitoring) given these interventions contain insecticides.

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
WHO in the WHO Inter Agency Manual for Malaria Control in Humanitarian Crises. Both tools are commercially available and ITPS has been widely used in many emergency settings in the last 10 years. • P. 21, line 27: It is not correct to say that Hammocks and treated clothing are the only "proven" alternatives to LLINs and IRS. Treated eve/door and window curtains are proven and well published. Treated plastic sheeting for temporary shelters are proven. All these are published, and all supported by WHO for use in emergency settings. They provide vital tools for malaria control amongst populations, especially the displaced, where shelter does not exist to spray, and where LLINs may not be feasible to install and hang. Please include these alternatives for use in emergency settings where needed. With 18 studies published from almost as many countries and three continents, there is currently significantly more proof that ITPS works, is applicable and is safe, than for Hammocks or treated clothing. Which is why its use in emergency contexts to build temporary shelters for refugees and internally displaced families is supported by the WHO Interagency Manual. Insecticide treated blankets also have proven effective for unsheltered refugees in Pakistan, and results are published by LSHTM. Studies in other geographic contexts are less developed. However, they logically work in the same basic manner as Hammocks, and there is a definite place for their use in some emergency contexts. • p. 22, line 1: One of the most important new tools under development and well supported by WHO is Durable Wall Lining. This is under Phase III testing (completed in Liberia) and ongoing in Tanzania with PMI support. It should be included here please. Results of Phase I, and multiple Phase II studies have already been • p. 24, line 3: The WHO position statement actually says that IRS coverage should be >80% not 85% (however, MENTOR Initiative always say and advise >85% for all programmes). *(NGO)*	Durable Wall Linings has been added as recommended.

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
	The text has been revised.
27. The outcome of the USAID assessment is significantly different to assessments performed previously by Syngenta and the WHO for Pirimiphos-methyl CS (Actellic 300 CS). Factors used in the risk assessment previously performed by Syngenta and accepted by the WHO are detailed below. Syngenta recommends USAID to revise the risk assessment performed for Pirimiphos-methyl taking into account the a.i. specific data on transferable residues and dermal absorption and the Syngenta position on endpoints. p .176: Syngenta propose the following endpoints, as the most appropriate for risk assessment of Actellic 300CS as a vector control product: Resident Chronic AEL = 0.025 mg/kg bw/day by applying a 10-fold uncertainty factor to the NOAEL of 0.25 mg/kg/day in the 56-day human volunteer study. Operator Chronic AEL = 0.05 mg/kg bw/day by applying a 5-fold uncertainty factor to the NOAEL of 0.25 mg/kg/day in the 56-day human volunteer study. These values are closely aligned with the reference doses agreed by the JMPR for Pirimiphos-methyl when used as a plant protection product (as shown below). JMPR Reference doses: ADI = 0.03 mg/kg bw/day by applying a 10-fold (10x Intraspecies) safety factor to the NOAEL of 0.25 mg/kg bw/day in the human studies. ARfD = 0.2 mg/kg bw by applying a 100-fold (10x intraspecies; 10x Interspecies) safety factor to the NOAL of 15 mg/kg bw/day in the Rat acute neurotox study. The use of resident and operator chronic AELs for risk assessment of Actellic 300CS, as a vector control product have been accepted by the WHO. (*Manufacturer*)	The 2006 WHO JMPR monograph summary of the human volunteer studies was reviewed. The monograph references an ADI of 0 – 0.03 mg/kg-d developed in 1992 based on the NOAEL of 0.25 mg/kg-d from the human studies. The 56-day human volunteer study was also applied by EPA in 1987 to develop a chronic oral RfD of 0.01 mg/kg-d which was published in the IRIS database. However, the IRIS value for pirimiphos-methyl was removed from IRIS and archived in July 2016 along with 50 other organophosphate pesticides. The current EPA toxicity benchmarks for pirimiphos-methyl are those developed by EPA's Office of Pesticide Programs (OPP) and used to support pesticide registration and food tolerances. These values are used in the PEA, consistent with the listing of toxicity benchmark references in Section 3.2.1. In EPA's 2009 "Pirimiphos-methyl: Human Health Assessment Scoping Document in Support of Registration Review" OPP summarized the selection of a key study for the risk assessment supporting the 2001 interim RED. This 2009 report indicates OPP considered the human volunteer study (Howard and Gore 1976) as a basis for developing an RfD but declined to do so due to what they described as technical limitations: "Human studies were used in endpoint selection for risk assessment for eight organophosphates, including pirimiphos-methyl. Using parameters developed for evaluation of human studies, HED (January, 1998) evaluated the 28-day oral study (Chart et al., 1974; MRID 00080747) and the 56-day oral study (Howard and Gore, 1976; MRID 00080732) in humans with pirimiphos-methyl. These studies were later classified as supplemental because the results provided useful scientific information that can be used as supportive data along with the results from the animal studies, but the studies alone are not sufficient for endpoint selection or risk assessments due to technical limitations. For the 1999 human health risk assessment, HED selected toxicology endpoints for pirimiphos-methyl based solely on animal toxicity studies."

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
28. p. 164, lines 1-2: Application rate for Actellic CS of 1.00E03 – 2.00E03 kg ai/m2 a. Should read E-03 instead of E03 (should be 1000 mg ai/m2) b. If the error has been used in any calculations it will have a big impact on the exposure assessments c. Other references to application rate in the document indicate the correct value (*Manufacturer*)	This is a typographical error. The Actellic CS application rate used in calculations is indeed 1000 mg/m2.
29. p. 211, last line: Fraction translodged onto skin: SYN propose the use of product specific data for dislodgeability from treated surfaces – a worst case mean value of 5.2%. WHO made use of the study data in their evaluation. A summary of the study is given in the document provided. (*Manufacturer*)	We appreciate that chemical-specific dislodgeability data exist for some products, but they are not available for most of the products analyzed here. We therefore opted to use the same standard value (0.14, the default material-to-skin transfer efficiency for treated paints and preservatives, EPA SOP 2012) for all products. Text has been added to acknowledge that this may result in overestimation of risks in some cases and that application of chemical-specific data could reduce risk estimates for some products.
30. p. 213, lines 8-9: Dermal absorption values: SYN propose the use of a.i. specific dermal absorption data (0.56% for concentrate and 8.5% for dilution). These values were agreed by WHO and applied to their evaluation. (*Manufacturer*)	Pesticide-specific dermal absorption values used in the risk assessments are those recommended by USEPA in the risk assessments supporting the toxicity benchmarks. EPA has not cited a dermal absorption value for pirimiphos-methyl in their 2016 exposure and risk assessment supporting registration review. If a study describing applicable dermal absorption data is available and can be provided for review, it will be evaluated in future PEA updates.
31. No significant additional comments – it is clear and the outcomes are meaningful. (*Manufacturer*)	n/a
32. p. 23, Table 2.1: Typo in the units for clothiandin WP and chlorfenapyr SC – should be 0.3 and 0.24 g/m2 respectively (*Manufacturer*)	These typographical errors have been corrected.
33. p. 22, last para: There is a statement that USAID procurement policies are that only products which are WHOPES recommended (have passed Phase 3 have spec published by JMPS) – this could be understood to contradict the scenarios described in Annex B ? (*Manufacturer*)	We have revised the narrative so there are no inconsistencies.
34. p. 21, Section 2.2: Part of sentence missing mid-paragraph? (*Manufacturer*)	We reviewed Section 2.2 and did not find an incomplete sentence, only a typo.
35. p. 40, Table 3.1: There is discrepancy between the values presented in Table 3-1 page 40 and the values presented in Annex F3 for UEinhal and UE derm. (*Manufacturer*)	Table 3.1 contained older values that were updated in Annex F3 for this PEA. The table has been revised to reflect current values.

COMMENT/QUESTION (*SOURCE*)	USAID RESPONSE
36. p. 9, lines 5-6: Refers to the 2011 revision of the WHO GRAM (for IRS) and the indicates the relevance of HAARP; which makes sense but what does this paragraph mean for products such as propoxur which have clearly not passed the Human Risk Assessment according to the 2011 WHO GRAM. Can situations exist where a product doesn't pass one but remains listed on the other? (*Manufacturer*)	Because the exposure models are harmonized with WHO GRAMs, significant differences between WHO assessments and those in the PEA are likely to arise only if the PEA and WHO apply different values for toxicity benchmarks. The PEA preferentially applies toxicity benchmarks published by OPP and these may differ from those selected by WHO.

ANNEX P: CLIMATE CHANGE

There is a consensus among climatologists that our planet is experiencing a progressive rise in surface temperature due to the increased production of "greenhouse" gasses. The Intergovernmental Panel on Climate Change predicts a rise of 1-3.5°C in global mean surface temperature by 2100. Several studies suggest that climate can affect infectious disease patterns because disease agents and their vectors are sensitive to temperature, moisture and other ambient environmental conditions. The extent of these effects continues to generate intense debate, especially in the projected effect of climate change on the global distribution of malaria, in which different modeling approaches have resulted in widely varying estimates.

Because temperature, precipitation and relative humidity are the main climatic factors that affect malaria transmission, they are the basis for the prediction of the effects of climate change on malaria. These relationships can be best understood in relation to the malaria life cycle. There are maximum, minimum and optimum temperatures (between 18°C - 32°C) for the development and survival of both the malaria parasite and the vector (i.e. the mosquito). The increases in temperature tend to show increases in feeding and egg laying frequency. The amount of precipitation affects the amount of surface water within which the vector can breed. Relative humidity (above 60%) lengthens the life of the mosquito, thereby helping the parasite complete the necessary life cycle so that it can transmit the infection.

Climate variability is widely considered to be a major driver of inter-annual variability of malaria incidence in Africa. The effects of temperature on both the vector and parasite of malaria are easily seen in latitudinal and altitudinal boundaries to malaria transmission. However, these boundaries seem to be changing as many highland areas have experienced malaria epidemics in the past few years. It has been hypothesized that increasing temperatures could partially explain the survival of malaria at higher altitudes. One projected scenario showed a potential increase of 5-7% in altitudinal malaria distribution with little increase in the latitudinal extents of the disease by 2100, although transmission may also decrease in other areas. The effect of the projected climate change indicates that a prolonged transmission season is as important as geographical expansion. At lower altitudes where malaria is already a problem, warmer temperatures will alter the growth cycle of the parasite in the mosquito enabling it to develop faster. This faster development will increase malaria transmission and therefore have implications on the burden of disease. Climate change could increase the epidemic potential of malaria in tropical countries currently susceptible to the disease.

In addition to climate change, there are other factors that may be responsible for changes in malaria incidence distribution that are important to note. These factors may include environmental modification (e.g. deforestation, irrigation, swamp drainage), population growth, limited access to health care, and lack of/or unsuccessful malaria control measures (Patz and Lindsay, 1999).

Despite the uncertainty, the findings from climate change studies have important programmatic implications for malaria vector control activities, and building vector control activities that are resilient to the impacts of climate change are critical and required under Executive Order 13653 (*Preparing the United States for the Impacts of Climate Change*). Duration and timing of the malaria season are critical to consider when conducting IRS, since IRS campaigns are ideally completed immediately before the rainy season to maximize protection during the rainy season, but not during the rainy season as roads often become impassible. Therefore, activity planners and program managers should consider climate-related data as plans for IRS campaigns are developed. Climate-related data can also be used as one factor (of several) in helping to assess reasons for malaria upsurges. For example, climate-related data, coupled with data on availability of commodities, an understanding of the local health service delivery provision, and similar factors, are important to consider if there is a malaria upsurge after a vector control campaign.