INTERACTION PROFILE FOR MIXTURES OF INSECTICIDES:

PYRETHROIDS, ORGANOPHOSPHORUS COMPOUNDS, AND CARBAMATES

Agency for Toxic Substances and Disease Registry
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PREFACE

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) mandates that the Agency for Toxic Substances and Disease Registry (ATSDR) shall assess whether adequate information on health effects is available for the priority hazardous substances. Where such information is not available or under development, ATSDR shall, in cooperation with the National Toxicology Program, initiate a program of research to determine these health effects. The Act further directs that where feasible, ATSDR shall develop methods to determine the health effects of substances in combination with other substances with which they are commonly found. The Food Quality and Protection Act (FQPA) of 1996 requires that factors to be considered in establishing, modifying, or revoking tolerances for pesticide chemical residues shall include the available information concerning the cumulative effects of substances that have a common mechanism of toxicity, and combined exposure levels to the substance and other related substances. The FQPA requires that the Administrator of the Environmental Protection Agency consult with the Secretary of the Department of Health and Human Services (which includes ATSDR) in implementing some of the provisions of the act.

To carry out these legislative mandates, ATSDR's Division of Toxicology and Human Health Sciences (DTHHS) has developed and coordinated a mixtures program that includes trend analysis to identify the mixtures most often found in environmental media, *in vivo* and *in vitro* toxicological testing of mixtures, quantitative modeling of joint action, and methodological development for assessment of joint toxicity. These efforts are interrelated. For example, the trend analysis suggests mixtures of concern for which assessments need to be conducted. If data are not available, further research is recommended. The data thus generated often contribute to the design, calibration or validation of the methodology. This pragmatic approach allows identification of pertinent issues and their resolution as well as enhancement of our understanding of the mechanisms of joint toxic action. All the information obtained is thus used to enhance existing or developing methods to assess the joint toxic action of environmental chemicals. Over a number of years, ATSDR scientists in collaboration with mixtures risk assessors and laboratory scientists have developed approaches for the assessment of the joint toxic action of chemical mixtures. As part of the mixtures program a series of documents, Interaction Profiles, are being developed for certain priority mixtures that are of special concern to ATSDR.

The purpose of an Interaction Profile is to evaluate data on the toxicology of the "whole" priority mixture (if available) and on the joint toxic action of the chemicals in the mixture in order to recommend approaches for the exposure-based assessment of the potential hazard to public health. Joint toxic action

includes additivity and interactions. A weight-of-evidence approach is commonly used in these documents to evaluate the influence of interactions in the overall toxicity of the mixture. The weight-of-evidence evaluations are qualitative in nature, although ATSDR recognizes that observations of toxicological interactions depend greatly on exposure doses and that some interactions appear to have thresholds. Thus, the interactions are evaluated in a qualitative manner to provide a sense of what influence the interactions may have when they do occur.

CONTRIBUTORS

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PEER REVIEW

A peer review panel was assembled for this profile. The panel consisted of the following members:

1. AMJ Ragas, Ph.D., Department of Environ Science, Faculty of Science, Radboud University Nijmegen, Netherlands.

2. Richard C. Hertzberg, Ph.D., Emory University, School of Public Health, Biomathematics Consulting, Atlanta, GA, USA.

3. Jane Ellen Simons, Ph.D., NHEERL, U.S. Environmental Protection Agency, Raleigh, NC, USA.

4. Bob Krieger, Ph.D., Department of Entomology, University of California, Riverside, CA, USA.

All reviewers were selected in conformity with the conditions for peer review specified in CERCLA Section 104(I)(13).

Scientists from ATSDR have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

SUMMARY

The purpose of this profile is to investigate the possible joint actions of pyrethroid insecticides, organophosphorus insecticides and carbamate insecticides on neurological end points in humans. In assessing the available information on possible interactions among these chemicals, this profile concludes with recommendations for conducting screening-level assessments of public health concerns from joint exposure to mixtures of these chemical classes.

ATSDR recommends that the default assumption of dose-additive joint action at shared targets of toxicity (i.e., effects on neurological end points) be used for screening-level assessments of the potential adverse health outcomes from concurrent oral exposures to mixtures of pyrethroids, organophosphorus and carbamate insecticides. The assessments should be accompanied by qualitative descriptions of weight-of-evidence evaluations of available interaction data:

1. greater-than-additive action on neurological end points is possible between certain pyrethroid and organophosphorus insecticides;

2. the available data are inadequate to assess the possible direction of interactions between pyrethroids and carbamates; and

3. limitations in evidence for greater-than-additive interactions support the assumption of dose additivity of carbamate and organophosphorus insecticides on neurological end points.

4. BINWOEs include scoring categories that address uncertainty in the data.

Overall, the evidence is not compelling to move from a dose-additive approach for screening-level assessments. The evaluations indicate that greater-than-additive interactions between certain pyrethroid and organophosphorus insecticides are possible, but key findings in mammals come from a study of potentiation of fenvalerate lethality in rats pretreated with certain organophosphorus insecticides (Gaughan et al. 1980). The relevance of these findings to relatively low (nonlethal) environmental concurrent exposure to pyrethroid and organophosphorus insecticides is not well understood.

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LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ATSDR	Agency for Toxic Substances and Disease Registry
BINWOE	binary weight-of-evidence
BPMC	2-sec-butylphenyl *N*-methylcarbamate
ChE	acetylcholinesterase
BMD	benchmark dose
BMDL	benchmark dose limit
BTEX	benzene, toluene, ethylbenzene, and xylene
CYP	cytochrome P450
DEF	S,S,S-tributyl phosphorotrithioate
DEET	N,N-diethyl-m-toluamide
DTHHS	Division of Toxicology and Human Health Sciences
EPA	U.S. Environmental Protection Agency
EPN	*O*-ethyl *O*-(4-nitrophenyl) phenyl phosphonothioate
ERDEM	exposure-related dose estimating model
FQPA	U.S. Food Quality and Protection Act
GABA	gamma-aminobutyric acid
GD	gestation day
HI	hazard index
HQ	hazard quotient
IARC	International Agency Research on Cancer
IR	interactive ratio
IRIS	Integrated Risk Information System
iso-OMPA	tetraisoproylpyrophosphoramide
kg	kilogram
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
mg	milligram
MOE	margin of exposure
MPMC	3,4-dimethylphenyl *N*-methylcarbamate
MRL	Minimal Risk Level
MTMC	3-methylphenyl *N*-methylcarbamate
NAC	1-naphthyl *N*-methylcarbamate
NOAEL	no-observed-adverse-effect level
NTE	neuropathy target esterase
NTP	National Toxicology Program
OPIDP	organophosphate-induced delayed polyneuropathy
OPP	U.S. EPA Office of Pesticide Programs
PBPK/PD	physiologically based pharmacokinetic/pharmacodynamic
PhAD	photic after discharge
PND	postnatal day
POD	point of departure
ppm	parts per million
RBC	red blood cell
RfD	reference dose
RPF	relative potency factor
TTD	target-organ toxicity dose
TU	toxic unit
U.S.	United States

VGSC	voltage-gated sodium channel
XMC	3,5-dimethylphenyl *N*-methylcarbamate
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to