INTERACTION PROFILE FOR:
ATRAZINE, DEETHYLATRAZINE, DIAZINON, NITRATE, AND SIMAZINE

U.S. Department of Health and Human Services
Public Health Service
Agency for Toxic Substances and Disease Registry

August 2006

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.

To carry out the legislative mandate, ATSDR's Division of Toxicology and Environmental Medicine (DTEM) 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.

ATSDR will use the following process for the development of interaction profiles:

- ATSDR will select substances/chemicals for development of interaction profiles through inter/intra agency communications and literature reviews.
- After the selection, a letter will be sent to individuals and agencies on ATSDR's mailing list providing notice of ATSDR's intent to create an interaction profile.
- A notice will also be posted in the Federal Register to inform the public of ATSDR's intent to develop a particular interaction profile.
- The draft interaction profile will undergo both internal and external peer review processes.
- A Federal Register notice will announce the release of the official draft for public comment.
- ATSDR will post a link to the draft interaction profile on its Website, giving the public an opportunity to provide comments.
- ATSDR will review all public comments and revise the draft, as appropriate, before issuing the final version.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS:

Hana Pohl, M.D., Ph.D.
ATSDR, Division of Toxicology and Environmental Medicine, Atlanta, GA

Joan Colman, Ph.D.
Syracuse Research Corporation, Syracuse, NY

PEER REVIEW

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

Dale Hattis, Ph. D.
The George Perkins Marsh Institute
Center for Toxicology, Environment, and Development
Clark University
Worcester, MA

Kannan Krishnan, Ph. D.
Department of Environmental and Occupational Health
Faculty of Medicine
University of Montreal, Montreal, QC, Canada

Sheldon Wagner, M.D.
Department of Environmental and Molecular Toxicology
Oregon State University
Corvallis, OR

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

Atrazine, deethylatrazine, simazine, diazinon, and nitrate were chosen as the subject mixture for this interaction profile because they frequently occur together in rural well water. Atrazine and simazine are triazine herbicides, deethylatrazine is a metabolite and an environmental degradation product of atrazine and other triazine herbicides, diazinon is an organophosphorus insecticide, and nitrate is a common contaminant resulting from fertilizers and human and animal waste. The exposures of greatest concern for this mixture in rural well water are intermediate and chronic oral exposures. No pertinent health effects data or physiologically-based pharmacokinetic (PBPK) models were located for the complete mixture. Therefore, the exposure-based screening assessment of potential health hazards for this mixture depends on an evaluation of the health effects and mechanistic data for the individual components and on the joint toxic action and mechanistic data for various combinations of the components. This profile discusses and evaluates the evidence for joint toxic action among atrazine, deethylatrazine, simazine, diazinon, and nitrate. The profile also discusses how public health assessments can incorporate concerns about interactions, additivity, and potential human exposures to mixtures of these chemicals.

Effects of concern for this mixture include reproductive effects (atrazine, deethylatrazine, and simazine), neurological effects (diazinon), and hematological effects (nitrate). Although none of the components has been classified as a carcinogen, atrazine and simazine can react with nitrite (nitrate metabolite) in the environment and *in vivo* to form N-nitrosoatrazine and N-nitrososimazine. Structure-activity considerations raise a concern for potential carcinogenicity of these nitrosamines. However, the issue of atrazine/nitrate and simazine/nitrate combinations and potential cancer risk in humans is still unresolved and further research is needed.

To screen the mixture of atrazine, deethylatrazine, simazine, diazinon, and nitrate for potential hazards to public health, the hazard quotients (ratios of exposures to health guidance values) are estimated for the individual components. If only one or if none of the components has a hazard quotient that is at least 0.1, no further assessment of the *joint toxic action* is needed because additivity and/or interactions are unlikely to result in significant health hazard. If the hazard quotients for two or more of the mixture components equal or exceed 0.1, the following procedures are recommended. To screen this mixture for potential reproductive health hazard, an endpoint-specific hazard index for reproductive effects should be estimated for atrazine, deethylatrazine, and simazine (the triazine components of the mixture). The weight-of-evidence (WOE) analysis for interactions among these components indicates high confidence in the additivity assumption that is the basis for the hazard index. The potential effect of diazinon and nitrate on

the reproductive toxicity of these triazines is uncertain. Separate hazard quotients are recommended to screen for the neurotoxicity of diazinon and the hematological toxicity of nitrate. The WOE analysis indicates that because the triazine components may potentiate the neurologic toxicity of diazinon, the hazard quotient for diazinon may tend to underestimate the hazard of exposure to diazinon when these triazine components are present. Confidence in these predictions is medium. No information regarding the impact of interactions on the hematological toxicity of nitrate was available, so uncertainty regarding the impact of the other components on this effect of nitrate is high.

If the reproductive hazard index for the triazines or the hazard quotient for nitrate is greater than 1, or if the hazard quotient for diazinon is close to or above 1, then further evaluation is needed (ATSDR 2001a), using biomedical judgment and community-specific health outcome data.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ATSDR	Agency for Toxic Substances and Disease Registry	NRC	Nuclear Regulatory Commission
BINWOE	binary weight-of-evidence	NTP	National Toxicology Program
CAS	Chemical Abstracts Service	PAD	population adjusted dose
CERCLA	Comprehensive Environmental Response, Compensation, and Recovery Act	2-PAM	pralidoxime
CHO	Chinese hamster ovary	PBPK	physiologically based pharmacokinetic
DACT	diaminochlorotriazine	PBPK/PD	physiologically-based pharmacokinetic/pharmacodynamic
DT	Division of Toxicology	ppb	parts per billion
EC_{50}	median effective concentration (produces desired effect in 50% of population)	RfC	reference concentration
EPA	Environmental Protection Agency	RfD	reference dose transaminase
FQPA	Food Quality Protection Act	SMR	standardized mortality ratio
GnRh	gonadotropin releasing hormone	TTD	target-organ toxicity dose
IARC	International Agency for Research on Cancer	µg	microgram
IRIS	Integrated Risk Information System	µmole	micromole
kg	kilogram	U.S.	United States
L	liter	VOC	volatile organic compound
LC_{50}	median lethal concentration (produces desired effect in 50% of the population)	WOE	weight-of-evidence
LH	luteinizing hormone		
LOAEL	lowest-observed-adverse-effect level	>	greater than
MCL	maximum contaminant level	≥	greater than or equal to
MCLG	maximum contaminant level goal	=	equal to
mg	milligram	<	less than
mM	millimole	≤	less than or equal to
MRL	Minimal Risk Level		
NADH	nicotinamide adenine dinucleotide phosphate		
ng	nanogram		
NOAEL	no-observed-adverse-effect level		