DRAFT

INTERACTION PROFILE FOR: CARBON MONOXIDE, FORMALDEHYDE, METHYLENE CHLORIDE, NITROGEN DIOXIDE, AND TETRACHLOROETHYLENE

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

August, 2007

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 (NTP), 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 these legislative mandates, 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.

CONTRIBUTORS

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PEER REVIEW

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

Arthur Gregory, Ph.D., DABT, Techno Enterprises, Luray, VA

Rolf Hartung, Ph.D., DABT, University of Michigan, Ann Arbor, MI

Kannan Krishnan, Ph.D., University of Montreal, Montreal, Canada

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

Carbon monoxide, formaldehyde, methylene chloride, nitrogen dioxide, and tetrachloroethylene were chosen as the subject for this interaction profile based on the likelihood of co-exposure to these chemicals in the home. Concentrations of these chemicals commonly are higher in indoor air than in outdoor air. Carbon monoxide is generated as a product of incomplete combustion from sources which include home furnaces and fireplaces. Formaldehyde is found in many products used around the house, such as antiseptics, medicines, cosmetics, dish-washing liquids, fabric softeners, shoe-care agents, carpet cleaners, glues and adhesives, lacquers, paper, plastics, and some types of wood products. Methylene chloride, also known as dichloromethane, is widely used as an industrial solvent and as a paint stripper and can also be found in certain aerosol and pesticide products, some spray paints, automotive cleaners, and other household products. High levels of nitrogen dioxide may be found in the home when unvented combustion appliances are used for cooking or heating (e.g., poorly-vented fireplaces or furnaces). Tetrachloroethylene may be found in the home environment as a result of dry cleaning operations, or when one or more of the members of the household works in processes involving tetrachloroethylene.

No pertinent health effects data or physiologically based pharmacokinetic (PBPK) models were located for the complete mixture. Therefore, as recommended by ATSDR (2001a) guidance, the exposure-based screening assessment of potential health hazards for this mixture depends on an evaluation of the health effects data 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 binary mixtures of these chemicals, and recommends how to incorporate concerns regarding possible interactions or additivity into public health assessments of people who may be exposed to mixtures of these chemicals.

There is no single endpoint that is a sensitive target of all components of the mixture. However, several endpoints are common across multiple chemicals within the mixture, including hematological effects, cardiovascular effects, respiratory effects, neurological alterations, hepatic injury, and cancer. With data on the individual components suggesting possible sites of joint toxic action, but no data available on the toxicity or behavior of the complete mixture or the relevant submixtures, a default component-based approach assuming additivity was therefore recommended.

Component-based approaches that assume additive joint toxic action are recommended for exposure-based assessments of possible noncancer or cancer health hazards from inhalation exposure to carbon monoxide, formaldehyde, methylene chloride, nitrogen dioxide, and tetrachloroethylene, because there

are no direct data available to characterize health hazards (and dose-response relationships) from the five-component mixture. The weight-of-evidence analysis indicated that data are inadequate to characterize the modes of joint action of many of the components, but the additivity assumption appears to be suitable in the interest of protecting public health since the components have several shared targets of toxicity (organs or organ systems that are individually affected by the components).

A target-organ toxicity dose (TTD) modification of the hazard index approach is recommended for conducting exposure-based assessments of noncancer health hazards. TTDs for several toxicity targets have been derived for each of the components, including TTDs for hematological, cardiovascular, respiratory, neurological, and hepatic effects. 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 index for any endpoint of concern is equal or greater than 1, then further evaluation is needed (ATSDR 2001a), using biomedical judgment and community-specific health outcome data, and taking into account community health concerns (ATSDR 1992).

For assessment of cancer risks from joint toxic action of the mixture, a similar component-based approach is recommended that involves multiplication of intakes of the components by U.S. Environmental Protection Agency (EPA) cancer slope factors and summation of the resultant risk estimates.

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LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry
BINWOE	binary weight-of-evidence
CAS	Chemical Abstracts Service
CDC	Centers for Disease Control and Prevention
CERCLA	Comprehensive Environmental Response, Compensation, and Recovery Act
CO	Carbon Monoxide
DT	Division of Toxicology
EPA	Environmental Protection Agency
FAO	Food and Agriculture Organization
FQPA	Food Quality Protection Act
HI	hazard index
IARC	International Agency for Research on Cancer
ip	intraperitoneal
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
iv	intravenous
kg	kilogram
L	liter
LC_{50}	median lethal concentration (produces desired effect in 50% of the population)
LD_{50}	median lethal dose (produces desired effect in 50% of the population)
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
mg	milligram
MRL	Minimal Risk Level
MTD	maximum threshold dose
NHANES	National Health and Nutrition Examination Survey
nM	nanomole
NO_2	Nitrogen Dioxide
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NTP	National Toxicology Program
OPP	Office of Pesticide Programs
PBPK	physiologically based pharmacokinetic
PBPK/PD	physiologically-based pharmacokinetic/pharmacodynamic
ppb	parts per billion
ppm	parts per million
RfC	reference concentration
RfD	reference dose
sc	subcutaneous
TTD	target-organ toxicity dose
µg	microgram
µmole	micromole
U.S.	United States
VOC	volatile organic compound
WHO	World Health Organization
WOE	weight-of-evidence
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to