

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

**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.

To carry out these legislative mandates, ATSDR's Office of Innovation and Analytics, Toxicology Section has developed and coordinated a mixtures program that includes trend analysis to identify the mixtures most often found in environmental media, locate available *in vivo* and *in vitro* toxicological studies evaluating mixtures, perform quantitative modeling of joint action, and develop methods 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 of 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 (WOE) approach is commonly used in these documents to evaluate the influence of interactions in the overall toxicity of the mixture. The WOE 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.

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PEER REVIEW

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

1. David C. Dorman, DVM, Ph.D., North Carolina State University, Raleigh, North Carolina.
2. Michael Aschner, Ph.D., Albert Einstein College of Medicine, New York, New York.
3. Richard Hertzberg, Ph.D., Biomathematics Consulting, Atlanta, Georgia.

These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for the compounds evaluated in this profile.

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 that include home furnaces and fireplaces. Formaldehyde is found in many products used around the house, such as antiseptics, medicines, cosmetics, dishwashing 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 drycleaning 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 (2001) 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, 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, using dose addition for noncancer endpoints and response addition for cancer endpoints. The weight-of-evidence (WOE) analysis indicated that data are inadequate to characterize the modes of joint action of many of the components, but the additivity assumption, especially dose additivity, 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, 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 dose additivity and/or interactions are unlikely to result in significant health hazard. If the hazard index for any endpoint of concern is ≥ 1 , then further evaluation is needed (ATSDR 2001), 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 exposure levels for each of the components by U.S. Environmental Protection Agency (EPA) cancer slope factors and summation of the resultant single chemical risk estimates.

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LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ADHD	attention-deficit/hyperactivity disorder
AQG	air quality guideline
ATSDR	Agency for Toxic Substances and Disease Registry
BINWOE	binary weight-of-evidence
CERCLA	Comprehensive Environmental Response, Compensation, and Recovery Act
CFD	computational fluid dynamics
CFK	Coburn-Forster-Kame
CHO	Chinese hamster ovary
CNS	central nervous system
COHb	carboxyhemoglobin
COPD	chronic obstructive pulmonary disease
CYP	cytochrome P450
DNA	deoxyribonucleic acid
EPA	U.S. Environmental Protection Agency
FDH	formaldehyde dehydrogenase
GSH	glutathione
GST- θ	glutathione S-transferase θ
GSTT1-1	theta-glutathione-S-transferase
HHS	Health and Human Services
HEC	human equivalent concentration
HPRT	hypoxanthine-guanine phosphoribosyl transferase
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
MFO	mixed function oxidase
MRL	Minimal Risk Level
NAAQS	National Ambient Air Quality Standard
NOAEL	no-observed-adverse-effect level
PBPK/PD	physiologically-based pharmacokinetic/pharmacodynamic
OR	odds ratio
POD	point of departure
R _f C	reference concentration
RNA	ribonucleic acid
TTD	target-organ toxicity dose
TWA	time-weighted average
WHO	World Health Organization
WOE	weight-of-evidence