INTERACTION PROFILE FOR CHLOROFORM, 1,1-DICHLOROETHENE, TRICHLOROETHYLENE, AND VINYL CHLORIDE

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

February 2026

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, locates available in *vivo* and in *vitro* toxicological studies evaluating mixtures, performs quantitative modeling of joint action, and develops 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 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. 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

Chloroform, 1,1-dichloroethene, trichloroethylene, and vinyl chloride were chosen as the subject mixture for this profile because they frequently occur in water around hazardous waste sites. The primary routes of exposure of nearby populations to mixtures of these volatile chemicals are likely to be inhalation and oral, and the durations of concern are intermediate and chronic. ATSDR toxicological profiles are available for all four of the components of the mixture (ATSDR 2019, 2022c, 2024a, 2024b); these documents are the primary sources of information presented in the Appendices concerning the toxicokinetics, health effects, mechanisms of action, and health guidelines for these chemicals.

The purposes of this profile are to: (1) evaluate data (if available) on health hazards, and their dose-response relationships, from exposure to this four-component mixture; (2) evaluate data on the joint toxic actions of components of this mixture; and (3) make recommendations for exposure-based assessments of the potential impact of joint toxic action of the mixture on public health.

No studies were located that examined health effects in humans or animals exposed to mixtures exclusively containing chloroform, 1,1-dichloroethene, trichloroethylene, and vinyl chloride, and no physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) models for this mixture have been developed. A component-based approach (ATSDR 2001, 2018) was applied, wherein the potential influence of individual components on the toxicity of other components in the mixture is evaluated. As joint action data are lacking for three of the six component pairs, the mechanisms of action for each component pair were also analyzed for evidence of potential joint toxic actions. The weight-of-evidence (WOE) analysis indicated that the most likely mode of joint action for the individual component pairs was competition for cytochrome P450 2E1 (CYP2E1) active sites, but only at high exposure levels where metabolic saturation may occur. Competitive inhibition of metabolism was predicted to result in less-than-additive toxicity for effects mediated through the generation of reactive metabolites (e.g., hepatic, renal, and carcinogenic effects), greater-than-additive toxicity for effects due to the toxicity of the parent compound (neurological effects of chloroform), and uncertain results for effects that may be due to both parent compound and metabolite (neurological effects of trichloroethylene) or have inadequate mechanistic data (neurological effects of vinyl chloride). Some evidence was available from acute-duration co-exposure studies in animals to support these predictions for hepatic effects.

Component-based approaches that assume endpoint-specific additive joint toxic action are recommended for exposure-based assessments of possible noncancer or cancer health hazards from inhalation exposure

to chloroform, 1,1-dichloroethene, trichloroethylene, and vinyl chloride, because there are no direct data available to characterize health hazards (and dose-response relationships) from the four-component mixture. The WOE analysis predicted nonadditive joint action at high exposure levels, but the mode of action (competitive inhibition of metabolism at saturating exposure levels) is not relevant to lower exposure scenarios, as would occur from exposures from water near hazardous waste sites; thus, the dose and response additivity assumptions appear to be suitable in the interest of protecting public health from noncancer and carcinogenic hazards, respectively.

The health effects or endpoints of concern for this mixture are hepatic and developmental effects (all four chemicals), renal (chloroform, 1,1-dichloroethene, trichloroethylene), neurological (chloroform, trichloroethylene, vinyl chloride), immunological (trichloroethylene, vinyl chloride), respiratory (chloroform, 1,1-dichloroethene), and cancer (chloroform, trichloroethylene, vinyl chloride). To screen this mixture for potential noncancer hazards to public health using the dose additivity approach, endpoint-specific hazard indexes are estimated using Minimal Risk Levels (MRLs) and target-organ toxicity doses (TTDs), derived in this interaction profile, for the exposure routes and durations of concern. This approach is appropriate when the hazard quotients for two or more of the mixture components equal or exceed 0.1. Endpoint-specific hazard indexes (e.g., hazard indexes for hepatic effects) for the same exposure duration (e.g., chronic) can be summed across routes (inhalation and oral) to estimate the aggregate hazard, if it is likely that the same individual or group of individuals would be exposed by both routes. The total cancer risk is estimated using the response addition approach, which involves summing the cancer risks for chloroform, trichloroethylene, and vinyl chloride. Cancer risks for the same exposure duration can be summed across routes if it is likely that the same individual or group of individuals would be exposed by both routes. If an endpoint-specific hazard index exceeds one, or the sum of the cancer risks for these chemicals equals or exceeds 1×10^{-4}, then further evaluation is needed (ATSDR 2018), using biomedical judgment and community-specific health outcome data, and considering community health concerns (ATSDR 1992). If exposures levels are very high interactions may occur (e.g., ≥100-fold above the MRLs or TTDs), and their potential impact on the hazard indexes and cancer risks can be determined using the WOE predictions discussed earlier in this summary.

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LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AKT	α-ketoglutarate transaminase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	area under the curve
BINWOE	binary weight-of-evidence
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
CERCLA	Comprehensive Environmental Response, Compensation, and Recovery Act
$CHCl_3$	chloroform
CNS	central nervous system
$COCl_2$	phosgene
CYP2E1	cytochrome P450 2E1
DCVC	S-(1,2-dichlorovinyl)-L-cysteine
DCVG	S-(1,2-dichlorovinyl)glutathione
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
GD	gestation day
GGT	gamma-glutamyl transferase
GSH	glutathione
GST	glutathione *S*-transferase
HCFC	hydrochlorofluorocarbon
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
IARC	International Agency for Research on Cancer
IgG	immunoglobulin G
IgM	immunoglobulin M
i.p.	intraperitoneal
LDH	lactate dehydrogenase
LOAEL	lowest-observed-adverse-effect level
LRRK2	leucine-rich repeat kinase 2
LSE	Levels of Significant Exposure
MFO	mixed function oxidase
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRL	Minimal Risk Level
NOAEL	no-observed-adverse-effect level
PBPK/PD	physiologically-based pharmacokinetic/pharmacodynamic
PFC	plaque-forming cell
POD	point of departure
PVC	polyvinyl chloride
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SDH	sorbitol dehydrogenase
SPL	Substance Priority List
SRBC	Sheep red blood cell

TaClo	trichloromethyl-1,2,3,4-tetrahydro-beta-carboline
TTD	target-organ toxicity dose
VOC	volatile organic compound
WOE	weight-of-evidence