1. Introduction

The primary purpose of this *Interaction Profile for Chloroform, 1,1-Dichloroethene, Trichloroethylene, and Vinyl Chloride* is to evaluate data on the toxicology of the "whole" mixture and the joint toxic action of the chemicals in the mixture in order to recommend approaches for assessing the potential hazard of this mixture to public health. To this end, the profile evaluates the whole mixture data (if available), focusing on the identification of health effects of concern, and adequacy and relevance of physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) models for the mixture. The profile also evaluates the evidence for joint toxic action—additivity and interactions—among the mixture components. A weight-of-evidence (WOE) approach is commonly used in these profiles to evaluate the influence of interactions in the overall toxicity of the mixture. The WOE evaluations are qualitative in nature, although the Agency for Toxic Substances and Disease Registry (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. The profile provides environmental health scientists with ATSDR Office of Innovation and Analytics, Toxicology Section recommended approaches for the incorporation of the whole mixture data or the concerns for additivity and interactions into an assessment of the potential hazard of this mixture to public health. These approaches can then be used with specific exposure data from hazardous waste sites or other exposure scenarios. For more information on different approaches to evaluating mixtures and background information on chemical interactions, readers can refer to the *Framework for Assessing Health Impacts of Multiple Chemical and Other Stressors* (ATSDR 2018).

The chloroform, 1,1-dichloroethene, trichloroethylene, and vinyl chloride mixture was chosen as the subject for this interaction profile because these chemicals were among the top 10 chemicals found in water around hazardous waste sites. They are currently at the 14th, 19th, 2nd, and 18th place, respectively, as determined by number of sites the chemicals were measured in water in ATSDR's Substance Priority List (SPL) data (ATSDR 2022a). Consequently, they are also encountered in combinations. All information provided here regarding the occurrence of these chemicals is extracted from the ATSDR's SPL data (ATSDR 2022a) and data are related to completed exposure pathways (i.e., people were/are actually exposed to the chemicals; for the definition of completed exposure pathways, see ATSDR 2022b). For example, the binary combination of 1,1-dichloroethene and trichloroethylene was reported at 91 sites in water (at 108 sites in all exposure media combined). Trichloroethylene and vinyl chloride combination occurred at 97 sites, of which 72 sites had these chemicals together in water. The binary

combination of chloroform and trichloroethylene was found in water at 63 sites (total 101 sites for all media). Chloroform and 1,1-dichloroethene were found together at 46 and 34 sites for total media and water, respectively. 1,1-Dichloroethene and vinyl chloride were reported at 44 sites; 36 sites had these chemicals in water media. Finally, the binary combination of chloroform and vinyl chloride was reported at 22 sites in water (40 sites for all media). Exposure to all four chemicals together occurred at 16 sites total and at 9 sites through contaminated water. Exposure levels detected in water at contaminated sites in 2022 are shown in Table 1.

Table 1. Levels of Pollutants at Contaminated Water Sites

Chemical (number of sites)	Median (mg/L)	Minimum (mg/L)	Maximum (mg/L)
Chloroform (147)	0.036	6.00×10^{-4}	7,800
1,1-Dichloroethene (91)	0.16	2.00×10^{-4}	910
Trichloroethylene (521)	5.85	9.80×10^{-7}	3,100,000
Vinyl chloride (58)	1.14	2.00×10^{-3}	1,000

Source: ATSDR (2022a)

Previously, ATSDR developed interaction profiles for other volatile organic compounds (VOCs) found frequently in water around hazardous waste sites. These include a mixture of 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene (ATSDR 2004a) and a mixture of benzene, ethylbenzene, toluene, and xylenes (ATSDR 2004b). Before evaluating the relevance of joint toxic action data for chloroform, 1,1-dichloroethene, trichloroethylene, and vinyl chloride, some understanding of these chemicals and the health endpoints of concern for inhalation and oral exposure is needed. The endpoints of concern include the various critical effects that are the bases for Minimal Risk Levels (MRLs) or other health guidance values, and any other endpoints that may become significant because they are relatively sensitive shared targets of toxicity or due to interactions (ATSDR 2018).

At room temperature, chloroform is a colorless, volatile liquid with a pleasant, nonirritating odor and slightly sweet taste. Chloroform may be found in the environment as a result of industrial production and use (mainly in the manufacture of the refrigerant, hydrochlorofluorocarbon-22 [HCFC-22]) or from generation of chloroform during water disinfection with chlorine. Following inhalation or oral exposure to chloroform, the most sensitive effects are on the liver and respiratory system; effects on the kidney, nervous system, and developing organism have also been reported. High-dose chloroform has been used as an anesthetic, but it is no longer used for that purpose. Many of chloroform's effects are believed to be the result of metabolism to active products that react with target tissues. The Department of Health and

Human Services' (HHS) *Fifteenth Report on Carcinogens* (NTP 2021a) states that chloroform is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals. The U.S. Environmental Protection Agency (EPA) has classified chloroform as *likely to be carcinogenic to humans* according to the 1999 cancer guidelines (EPA 1999) based on sufficient evidence of carcinogenicity in animals at sufficiently high exposure conditions that produce sustained cytotoxicity and regenerative hyperplasia (EPA 2001). The International Agency for Research on Cancer (IARC) classifies chloroform as *possibly carcinogenic to humans* (Group 2B) based on inadequate evidence in humans and sufficient evidence in experimental animals (IARC 1999). More information on chloroform is provided in Appendix A and ATSDR (2024a).

At room temperature, 1,1-dichloroethene is a colorless, highly volatile liquid with a mild, sweet smell. The primary source of 1,1-dichloroethene in the environment is industrial production and use (to make polyvinylidene chloride copolymers for plastics, flexible wraps, and flame-retardant coatings). 1,1-Dichloroethene's primary effects following exposure are on the respiratory tract (inhalation), liver, kidney, and developing organism. Many of 1,1-dichloroethene's effects are believed to be the result of metabolism to active products that react with target tissues. The HHS *Fifteenth Report on Carcinogens* (NTP 2021b) does not list 1,1-dichloroethene. EPA (2002) has classified 1,1-dichloroethene (listed as 1,1-dichloroethylene) as having *suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential* via the inhalation route according to the 1999 cancer guidelines (EPA 1999) based on animal data (data are inadequate to assess its carcinogenic potential via the oral route). IARC (2019) notes that 1,1-dichloroethene (listed as vinylidene chloride) is *possibly carcinogenic to humans* (Group 2B) based on sufficient evidence in experimental animals. More information on 1,1-dichloroethene is provided in Appendix B and ATSDR (2022c).

At room temperature, trichloroethylene is a colorless, volatile liquid with a somewhat sweet odor. It is used primarily as a solvent and may be found in numerous industrial applications as well as in paint removers, adhesives, and spot removers. Following inhalation or oral exposure, trichloroethylene is metabolized to active metabolites including trichloroacetic acid and trichloroethanol. The primary effects of trichloroethylene and its metabolites are neurological (altered visual-motor coordination, drowsiness), and additional effects by the metabolites including hepatic, renal, immunological, and developmental are also reported. The HHS *Fifteenth Report on Carcinogens* (NTP 2021c) states that trichloroethylene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence from human studies. EPA (2011) classified trichloroethylene as *carcinogenic to humans* according to the 2005 cancer guidelines (EPA 2005) based on sufficient epidemiological evidence. IARC (2014) lists trichloroethylene as

Group 1 (*carcinogenic to humans*) based on sufficient evidence in humans and experimental animals. More information on trichloroethylene is provided in Appendix C and ATSDR (2019).

Vinyl chloride is a colorless gas at room temperature, which at very high concentrations, has a mild, sweet odor. It is commonly used industrially, mainly in the production of polyvinyl chloride (PVC) polymers. The majority of its effects are believed to result from metabolism to active intermediates, which then react with target tissues. The most sensitive effects of inhalation or oral exposure to low levels of vinyl chloride have been reported in the liver; immunological, neurological, and developmental effects also have been reported following inhalation exposures. The HHS *Fifteenth Report on Carcinogens* (NTP 2021d) reports that vinyl chloride is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans. EPA (2000) classified vinyl chloride as a *known/likely human carcinogen* according to the proposed 1996 cancer guidelines (EPA 1996) based on epidemiological data. IARC (2012) lists vinyl chloride as *carcinogenic to humans (Group 1*) based on sufficient evidence of carcinogenicity in humans and animals. More information on vinyl chloride is provided in Appendix D and ATSDR (2024b).

ATSDR toxicological profiles are available for all four of the chemicals that make up the mixture (ATSDR 2019, 2022c, 2024a, 2024b); these documents are the primary source of information presented in the appendices concerning the toxicokinetics, health effects, mechanisms of action, and health guidelines for these chemicals. The various critical effects that are the bases for the MRLs, as well as other relatively sensitive effects, are summarized in Table 2. All four chemicals are known to have effects on the liver and developing organism. The nervous and renal systems are common targets of three of the chemicals, and the immunological and respiratory systems are common targets of two of the chemicals. Carcinogenicity is an endpoint of concern for three of the chemicals. No pertinent studies of the toxicity or interactions of, or of PBPK models for, the complete mixture or any of the tertiary submixtures were located. Limited joint toxic action data are available for three of the individual component binary mixtures, and metabolic data and PBPK models are available for three of the binary mixtures.

Table 2. Potential Sensitive Health Effects of Concern for Intermediate- and Chronic-Duration Inhalation and Oral Exposure to the Mixture, Chloroform, 1,1-Dichloroethene, Trichloroethylene, and Vinyl Chloride[a,b]

Endpoint	Chloroform	1,1-Dichloroethene	Trichloroethylene	Vinyl chloride
Hepatic	**X**	**X**	X	**X**
Renal	X	X	X	
Immunological			**X**	X[c]
Respiratory	**X**[c]	**X**[c]		
Neurological	X		X	X
Developmental	X	X	**X**	X[c]
Cancer	X		X	X

[a]See Appendices A, B, C, and D.
[b]The basis for the intermediate- and chronic-duration MRLs are bolded; other sensitive effects are listed in regular typeface.
[c]Inhalation only.