1. INTRODUCTION

The primary purpose of this Interaction Profile for chloroform, 1,1-dichloroethylene, 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, adequacy of the data as the basis for a mixture Minimal Risk Level (MRL), 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 weight-of-evidence 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 Division of Toxicology and Environmental Medicine's (DTEM) 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.

The chloroform, 1,1-dichloroethylene (DCE), trichloroethylene (TCE), and vinyl chloride (VC) mixture was chosen as the subject for this interaction profile because these chemicals are among the top ten chemicals found in water around hazardous waste sites. They are at the 9th, 7th, 1st, and 8th place, respectively. Consequently, they are also encountered in combinations. All information provided here regarding the occurrence of these chemicals is extracted from the ATSDR's HazDat database (ATSDR 2006) and data are related to completed exposure pathways, i.e., people were/are actually exposed to the chemicals (for definition see ATSDR 1992). For example, the binary combination of 1,1-dichloroethylene and trichloroethylene is the 3rd most often found in contaminated waters and was reported at 62 sites (at 70 sites in all exposure media combined). The binary combination of chloroform and trichloro-

ethylene was found in water at 52 sites which represents the 8th place of occurrence (total 61 sites for all media). Chloroform and 1,1-dichloroethylene were found together at 34 and 28 sites for total media and water, respectively. Trichloroethylene and vinyl chloride combination occurred at 54 sites of which 46 sites had these chemicals together in water. 1,1-Dichloroethylene and vinyl chloride were reported at 25 sites; 23 sites had the chemicals in water media. Finally, the binary combination of chloroform and vinyl chloride was reported at 13 sites in water (19 sites for all media). Exposure to all four chemicals together occurred at 8 sites total and at 6 sites through contaminated water. Previously, ATSDR has developed interaction profiles for other VOCs found frequently in water around hazardous waste sites. These include a mixture of 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene and a mixture of benzene, ethylbenzene, toluene, and xylenes (www.atsdr.cdc.gov/interactionprofiles/).

Before evaluating the relevance of joint toxic action data for these chemicals, some understanding of these chemicals and the health endpoints of concern for inhalation and oral exposure is needed. The endpoints of concern include the critical effects that are the bases for 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 2004a).

At room temperature, chloroform is a colorless, volatile liquid with a pleasant, nonirritating odor and a 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 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; effects on the kidney, immune system, nervous system, and the developing organism have also been reported. High-dose chloroform has been used as an anesthetic, but 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 National Toxicology Program's (NTP) Eleventh Report on Carcinogens (NTP 2005) states that chloroform is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals. The International Agency for Research on Cancer (IARC 1999a) classifies chloroform as *possibly carcinogenic to humans* (Group 2B) based on inadequate evidence in humans and sufficient evidence in experimental animals. EPA (IRIS 2005) has classified chloroform as *reasonably anticipated to be a human carcinogen* (Group 2B). More information on chloroform is provided in Appendix A and by ATSDR (1997a).

At room temperature, 1,1-dichloroethylene is a colorless, highly volatile liquid with a mild, sweet smell. The primary source of 1,1-dichloroethylene in the environment is industrial production and use (to make polyvinylidene chloride copolymers for plastics, flexible wraps, and flame retardant coatings). 1,1-Dichloroethylene's primary effects following inhalation exposure are on the liver, although effects on the kidney and the developing organism have also been reported. Many of 1,1-dichloroethylene's effects are believed to be the result of metabolism to active products that react with target tissues. The NTP's Eleventh Report on Carcinogens (NTP 2005) does not list 1,1-dichloroethylene. The International Agency for Research on Cancer (IARC) (1999b) notes that 1,1-dichloroethylene is *not classifiable as to its carcinogenicity to humans* (Group 3). EPA (IRIS 2005) has classified 1,1-dichloroethylene as carcinogenicity Group C (*possible human carcinogen*). More information on 1,1-dichloroethylene is provided in Appendix B and by ATSDR (1994).

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 remover, adhesives, and spot removers. Following inhalation or oral exposure, the primary effects of trichloroethylene are neurological (altered visual-motor coordination, drowsiness), with other effects including hepatic, renal, immunological, and developmental also reported. The NTP's Eleventh Report on Carcinogens (NTP 2005) states that trichloroethylene is *reasonably anticipated to be a human carcinogen*. Trichloroethylene, is listed as Group 2A (*possibly carcinogenic to humans*) by IARC, and has not been given a cancer classification by EPA (IRIS 2005). More information on trichloroethylene is provided in Appendix C and by ATSDR (1997b).

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, and for inhalation exposures, renal, immunological, and developmental effects also have been reported. Neurological effects have been reported from very high inhalation exposures. The NTP's Eleventh Report on Carcinogens (NTP 2005) reports that vinyl chloride is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans. IARC (1987) lists vinyl chloride in Group 1 (*carcinogenic to humans*) based on sufficient evidence of carcinogenicity in humans and animals. Vinyl chloride is a *known human carcinogen* (Group A) under the EPA (IRIS 2005) classification scheme. More information vinyl chloride is provided in Appendix D and by ATSDR (2004b).

The critical effects that are the bases for the MRLs, as well as other relatively sensitive effects, are summarized in Table 1. All four chemicals are known to have effects on the liver, kidney, and developing organism. The immunological system is a common target of three of these chemicals, and the nervous system of two. 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. ATSDR toxicological profiles are available for all four of the chemicals that make up the mixture (ATSDR 1994, 1997a, 1997b, 2004b); 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.

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

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

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