3. Recommendation for Exposure-Based Assessment of Joint Toxic Action of the Mixture

1,1,1-Trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene frequently occur together in water samples, and in air samples to a less frequent extent, collected from hazardous waste sites. As discussed in Chapter 2 and the Appendices, each of the chemicals can produce neurological impairment via parent compound-induced physical and chemical changes in neuronal membranes and cause noncarcinogenic and carcinogenic responses (via reactive metabolites) in the liver and kidneys of animals. Each of the chemicals is volatile and has good solvent properties. Confidence is high that all of these chemicals are rapidly eliminated from the body based on human and animal toxicokinetic studies for three of the chemicals (1,1,1-trichloroethane, trichloroethylene, and tetrachloroethylene) and animal studies for the fourth (1,1-dichloroethane) (Appendices A, B, C, and D). There are data to indicate that some accumulation in fat can occur due to the lipophilicity of the compounds, but elimination half-lives from fat (the tissue type with the longest elimination half-lives) have been estimated on the order of hours (e.g., Monster et al. 1976, 1979), compared with much longer half-lives for biopersistent compounds such as polychlorinated biphenyls. Only one of the four, trichloroethylene, is extensively metabolized; the remaining three are predominately excreted unmetabolized in exhaled breath.

Neurological impairment forms the basis for each of ATSDR's MRLs for these chemicals, regardless of exposure route or duration (Table 4). Although some evidence of cancer, of varying weight, has been found in animal studies for each of these chemicals, low level exposure of humans may not present high risks for cancer. EPA (IRIS 2001) assigned 1,1,1-trichloroethane to Cancer Group D (Not Classifiable as to Human Carcinogenicity), 1,1-dichloroethane to Cancer Group C (Possible Human Carcinogen), and trichloroethylene and tetrachloroethylene to the boundary between Group C (Possible Human Carcinogen) and Group B2 (Probable Human Carcinogen). EPA lists no oral slope factors or inhalation unit risks for these chemicals on its IRIS (2001) database. The National Toxicology Program (NTP 2001) list of chemicals reasonably anticipated to be human carcinogens includes trichloroethylene and tetrachloroethylene, but not 1,1-dichloroethane or 1,1,1-trichloroethane. IARC (2001) has not assigned a cancer classification for 1,1-dichloroethane, but assigned 1,1,1-trichloroethane to Cancer Group 3, not classifiable as to human carcinogenicity, and trichloroethylene and tetrachloroethylene to Cancer Group 2A, probably carcinogenic to humans.

To conduct exposure-based assessments of possible health hazards from exposures to mixtures of these chemicals, a component-based Hazard Index approach is recommended, because there are no direct data

available to characterize health hazards (and dose-response relationships) from exposure to the mixture. Furthermore, PBPK models have not yet been developed that would predict appropriate target doses of the components from exposure to the mixture; such models would be useful in assessing health hazards from exposure to the mixture. As discussed by ATSDR (1992, 2001a), exposure-based health assessments are used, in conjunction with evaluation of community-specific health outcome data, consideration of community health concerns, and biomedical judgement, to assess the degree of public health hazard presented by mixtures of hazardous substances released into the environment.

To calculate hazard indices for each exposure scenario of concern, hazard quotients (i.e., the ratio of an exposure estimate to the appropriate MRL; see Appendices for MRLs) should first be calculated for each of the components (see Figure 2 in *Guidance Manual for the Assessment of the Joint Toxic Action of Chemical Mixtures*, ATSDR 2001a). If two or more of the individual components have hazard quotients equaling or exceeding ratios of 0.1, then the assessment should proceed. If only one or if none of the components have a hazard quotient that equals or exceeds 0.1, then no further assessment of the joint toxic action is needed because additivity and/or interactions are unlikely to result in significant health hazard. As exposure levels approach threshold levels for toxic effects, a hazard index approach is likely to give a more accurate assessment of health hazards than an approach that only examines hazard quotients for individual components in a mixture, as evidenced by results showing that liver endpoints were adversely affected by exposure to binary or ternary mixtures of trichloroethylene, tetrachloro-ethylene, and 1,1,1-trichloroethane at dose levels of the components that were near, but below, threshold levels for the individual (Stacey 1989). Under conditions for proceeding with the hazard index approach, the hazard quotients are summed to derive the hazard index as follows:

$$HI = \frac{E_{TCA}}{MRL_{TCA}} + \frac{E_{DCA}}{MRL_{DCA}} + \frac{E_{TCE}}{MRL_{TCE}} + \frac{E_{PERC}}{MRL_{PERC}}$$

where *HI* is the hazard index (a different hazard index is derived for each duration of exposure—acute, intermediate, and chronic—and each exposure route of concern), *E* represents the exposure estimates for the individual components, MRL represents the appropriate minimal risk levels for the components, and TCA, DCA, TCE, and PERC represent 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene. Because there are no ATSDR MRLs (or EPA RfDs or RfCs) for 1,1-dichloroethane for any exposure duration or route, hazard quotients for this chemical cannot be calculated. Because all of the MRLs for these chemicals are based on neurological impairment as the critical effect, the calculated hazard indices will provide indicators of the hazard for neurological impairment. Preliminary evidence

that the exposure to the mixture may constitute a hazard for neurological impairment is provided when the hazard index for a particular exposure scenario exceeds one. In practice, concern for the possibility of a health hazard increases with increasing value of the hazard index above 1.

The addition of hazard quotients for a particular exposure scenario assumes that the mixture components additively act on a common toxicity target by a common mechanism or mode of action, and that less-than-additive (e.g., antagonistic interactions) or greater-than-additive (e.g., synergism or potentiation) interactions do not occur among the components of the mixture. A primary objective of this profile was to assess available information on modes of joint toxic actions of 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene. As discussed in Section 2.3, a weight-of-evidence approach was used to evaluate the possible influence of interactions in the overall toxicity of the mixture. Twelve BINWOE determinations were made for the mode of joint action on the nervous system by the six pairs of the chemicals. As shown in Table 17, each of the BINWOEs for nervous system effects determined an additive joint action with data quality factors of "II" to reflect moderate mechanistic understanding supporting the plausibility of joint additive action (without interactions) and "C" to reflect the lack of direct toxicological data to test the hypothesis of joint additive action on the nervous system. The BINWOE determinations are taken to be applicable to all routes and durations of exposure because neurological effects are the basis for all of ATSDR's MRLs for these chemicals, regardless of exposure route or duration. In summary, it is plausible that 1,1,1-trichloroethane, 1,1,-dichloroethane, trichloroethylene, and tetrachloroethylene jointly act in an additive manner to impair nervous system function based on mechanistic understanding that the parent chemicals and a metabolite (trichloroethanol), like other lipophilic solvents, produce reversible chemical and physical changes in neuronal membranes that impair their functions. No evidence was found to indicate that the components may jointly act on the nervous system in a less-than-additive or greater-than-additive mode, but studies directly designed to examine the mode of joint toxic action of these chemicals on the nervous system were not located.

BINWOE determinations were made for the joint toxic actions of binary combinations of the mixture components on the liver and kidney, in anticipation of public health concerns that there may be greater-than-additive interactions that might cause liver and kidney effects to occur. Additive joint action was selected as plausible in 11 of 12 BINWOE considerations (see Tables 5–16 and Table 18) based on plausibility from mechanistic understanding and/or limited evidence from rat studies of joint action of binary mixtures on liver and kidney endpoints. The effect of tetrachloroethylene on trichloroethylene's hepato and renal toxicity (the twelfth BINWOE) was projected to occur by a less-than-additive joint action based on *in vivo* evidence that tetrachloroethylene inhibits the metabolism of trichloroethylene in

humans under occupational exposure conditions (Seiji et al. 1989), and evidence that trichloroethylene and tetrachloroethylene act in a less-than-additive manner to cause hepatic and renal peroxisomal proliferation (Goldsworthy and Popp 1987). In summary, the available data provide no evidence of greater-than-additive interactions among 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, or tetrachloroethylene that might cause liver and kidney effects to occur.