3. RECOMMENDATION FOR EXPOSURE-BASED ASSESSMENT OF JOINT TOXIC ACTION OF THE MIXTURE

As discussed above, the mixture of chloroform, 1,1-dichloroethylene, trichloroethylene, and vinyl chloride was chosen as the subject for this interaction profile because these chemicals frequently occur in water around hazardous waste sites. The exposure scenarios of greatest concern for the complete mixture are likely to be inhalation (owing to the volatility of the individual components) and oral exposure for intermediate and chronic durations.

Because suitable data, joint action models, and PBPK models are lacking for the complete mixture, the recommended approach for the exposure-based assessment of joint toxic action of this mixture for non-cancer endpoints is to use the hazard index method with the TTD modification and qualitative WOE method to assess the potential consequences of additive and interactive joint action of the components of the mixture. These methods are to be applied only under circumstances involving significant exposure to the mixture, i.e., only if hazard quotients for two or more of the compounds equal or exceed 0.1 (Figure 2 of ATSDR 2004a). Hazard quotients are the ratios of exposure estimates to noncancer health guideline values, such as MRLs. If only one or if none of the compounds 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 discussed by ATSDR (2004a), the exposure-based screening for potential health hazard is used in conjunction with biomedical judgment, community-specific health outcome data, and community health concerns to assess the degree of public health hazard.

The TTD modification of the hazard index requires the estimation of route, duration, and endpoint-specific (target-organ-specific) hazard indexes for the endpoints of concern for a particular mixture. The noncancer endpoints of concern for a mixture are the critical effects of the individual components, and toxicity targets in common that may become significant due to additivity or interactions. For this mixture, the endpoints of concern are hepatic, renal, immunological, neurological, and developmental effects. Therefore, these endpoints are candidates for TTD development for the components of this mixture. The TTDs were derived as described in the Appendices to this document, using the methods recommended by ATSDR (2001, 2004a). BINWOEs have been developed for these endpoints also, as presented in Section 2.3, and summarized later in Section 3. The derived TTD values for intermediate inhalation exposure are listed in Table 21, which also lists the intermediate inhalation MRLs for each chemical.

Table 21. MRLs and TTDs for Intermediate Inhalation Exposure to Chemicals of Concern[a]

	Chemical			
Endpoint	Chloroform (ppm)	1,1-Dichloroethylene (ppm)	Trichloroethylene (ppm)	Vinyl chloride (ppm)
Hepatic	0.05 (intermediate MRL)	0.02 (intermediate MRL)	1	0.03 (intermediate MRL)
Renal	0.05	0.04	0.7	0.07
Immunological	0.05	Not applicable	0.1	0.03
Neurological	0.05	Not applicable	0.1 (intermediate MRL)	NA
Developmental	0.05	0.05	3	0.5 (acute MRL)

[a]See Appendices A, B, C, and D

With the exception of chloroform, adequate chronic inhalation data are not available for most of the endpoints of concern for the chemicals that make up the mixture. However, as described in the Appendices to this document, the pharmacokinetics of the compounds are similar, with the compounds in general being rapidly absorbed, metabolized by the same enzymes, and eliminated reasonably rapidly from the body. As such, chloroform was used as the model chemical for consideration of chronic TTDs, and chronic TTD values for chloroform were derived in Appendix A. The chronic inhalation MRL for chloroform is 0.02 ppm and the intermediate inhalation MRL is 0.05 ppm, with both being based on similar physiological effects. As this difference is approximately half an order of magnitude ($10^{0.5}$) and because of the pharmacokinetic similarities and similar mode of action among the chemicals of the mixture, it is recommended that only for this mixture and the inhalation route, when chronic data are lacking, the intermediate inhalation TTDs and MRLs for 1,1-dichloroethylene, trichloroethylene, and vinyl chloride be adjusted using a modifying factor of 3 ($10^{0.5}$) when being considered in a chronic exposure scenario. The chronic inhalation TTD values are presented in Table 22, along with the chronic inhalation MRL for chloroform.

Table 22. MRLs and TTDs for Chronic Inhalation Exposure to Chemicals of Concern[a]

Endpoint	Chemical			
	Chloroform (ppm)	1,1-Dichloroethylene (ppm)	Trichloroethylene (ppm)	Vinyl chloride (ppm)
Hepatic	0.02 (chronic MRL)	0.007	0.3	0.01
Renal	0.02	0.04	0.7	0.07
Immunological	0.02	Not applicable	0.03	0.01
Neurological	0.03	Not applicable	0.03	Not applicable
Developmental	0.03	0.02	1	0.2

[a]See Appendices A, B, C, and D

TTDs also were derived for oral exposure as described in the Appendices to this document, using the methods recommended by ATSDR (2001, 2004a), and are listed, along with MRLs, in Table 23 for intermediate exposure and Table 24 for chronic exposure.

Table 23. MRLs and TTDs for Intermediate Oral Exposure to Chemicals of Concern[a]

Endpoint	Chemical			
	Chloroform (mg/kg/day)	1,1-Dichloroethylene (mg/kg/day)	Trichloroethylene (mg/kg/day)	Vinyl chloride (mg/kg/day)
Hepatic	0.01 (intermediate MRL)	0.3	3	0.003
Renal	0.1	0.3	2	Not applicable
Immunological	0.1	Not applicable	2	Not applicable
Neurological	0.3	Not applicable	0.08	Not applicable
Developmental	0.1	0.3	0.1	Not applicable

[a]See Appendices A, B, C, and D.

Table 24. MRLs and TTDs for Chronic Oral Exposure to Chemicals of Concern[a]

	Chemical			
Endpoint	Chloroform (mg/kg/day)	1,1-Dichloroethylene (mg/kg/day)	Trichloroethylene (mg/kg/day)	Vinyl chloride (mg/kg/day)
Hepatic	0.01 (chronic MRL)	0.009 (chronic MRL)	3	0.003 (chronic MRL)
Renal	0.1	0.009	2	Not applicable
Immunological	0.01	Not applicable	2	Not applicable
Neurological	0.03	Not applicable	0.008	Not applicable
Developmental	0.04	0.009	0.1	Not applicable

[a]See Appendices A, B, C, and D.

A hazard index is calculated for each effect, route, and exposure duration of concern, using the MRLs and TTDs listed in Tables 21, 22, 23, and 24, or newer values as they become available. This process is shown, using intermediate-duration inhalation hepatic effects as an example, in the following equation:

$$HI_{HEPATIC} = \frac{E_{CHCl_3}}{MRL_{CHCl_3}} + \frac{E_{DCE}}{MRL_{DCE}} + \frac{E_{TCE}}{TTD_{TCE,HEPATIC}} + \frac{E_{VC}}{MRL_{VC}}$$

where $HI_{HEPATIC}$ is the intermediate-duration inhalation hazard index for hepatic toxicity, E_{CHCl3} is the intermediate inhalation exposure to chloroform (in ppm), MRL_{CHCl3} is the intermediate inhalation MRL for chloroform (based on hepatic effects, in ppm), E_{DCE} is the intermediate inhalation exposure to 1,1-dichloroethylene (in ppm), MRL_{DCE} is the intermediate inhalation MRL for 1,1-dichloroethylene (based on hepatic effects, in ppm), E_{TCE} is the intermediate inhalation exposure to tetrachloroethylene (in ppm), $TTD_{TCE,HEPATIC}$ is the intermediate inhalation TTD for hepatic effects of TCE (in ppm), E_{VC} is the intermediate inhalation exposure to vinyl chloride (in ppm), and MRL_{VC} the intermediate inhalation MRL for vinyl chloride (based on hepatic effects, in ppm). The process can be then repeated for each endpoint of concern for intermediate inhalation exposure, using the appropriate exposure concentrations and TTDs/MRLs, resulting in endpoint-specific hazard indices for each effect of concern for the mixture. The same process can be carried out for chronic inhalation exposure, using chronic exposure concentrations and chronic inhalation TTDs and MRLs, and for intermediate and chronic oral exposure, for which the exposures are estimated as oral intakes in mg/kg/day, consistent with the units of the intermediate and chronic oral MRLs and TTDs. Components for which data are not available, or which do not affect the endpoint, are not included in the endpoint-specific hazard index calculations.

If the hazard index for effects on an endpoint of concern for any duration and route exceeds one, it provides preliminary evidence that the mixture may constitute a health hazard due to the joint toxic action of components on that endpoint (ATSDR 2004a). The impact of interactions from the WOE analysis also is considered. For this particular mixture, the available data on the component pairs support less-than-additive interactions for the individual pairs for most endpoints, as shown in Table 25; for neurological effects of chloroform, the available mechanisms suggest greater-than-additive interactions, and for the neurological effects of trichloroethylene, the direction of interaction is indeterminate. However, since the mechanism behind the interaction is likely to only occur at very high (100-fold or more times the corresponding MRL or TTD values) exposure levels, it is not likely to be a significant contributor at exposure levels resulting from water near hazardous waste sites.

If this screening procedure indicates preliminary evidence of a mixture health hazard, additional evaluation is needed to assess whether a public health hazard exists (ATSDR 2004a). The additional evaluation includes biomedical judgment, assessment of community-specific health outcome data, and consideration of community health concerns (ATSDR 1992).

The default approach for a multi-component mixture for which no data on the carcinogenicity of the mixture are available and no PBPK models have been validated, involves summing the component cancer risks. The carcinogenic risk for each component is calculated by multiplying lifetime inhalation and oral exposure estimates for each component by the appropriate EPA cancer inhalation unit risk (an estimate of cancer risk per unit of exposure) and oral slope factor, respectively. If only one or if none of the component risks equals or exceeds $1x10^{-6}$, then no further assessment of joint toxic action is needed due to the low likelihood that additivity and/or interactions would result in a significant health hazard. The nonadditive interactions between the components are not likely to be significant factors at the generally low exposure levels encountered from contaminated water near hazardous waste sites. Cancer risk can be estimated only for chloroform and vinyl chloride, because no unit risk or slope factor is available for tri-chloroethylene. If the sum of the cancer risks for these components for any route and duration of exposure equals or exceeds $1x10^{-4}$, then further evaluation is needed (ATSDR 2004a), using biomedical judgment and community-specific health outcome data, and taking into account community health concerns (ATSDR 1992).

Table 25. Matrix of BINWOE Determinations for Simultaneous Exposure to High Levels of Chemicals of Concern[1]

		ON THE TOXICITY OF			
EFFECT OF		Chloroform	1,1-Dichloroethylene	Trichloroethylene	Vinyl chloride
	Chloroform		<IIBb h,r,d	<IAii h <IBii r,i,d,c ? n	<IIBb h,r,i,d,c
	1,1-Dichloro-ethylene	<IIBb h,r,i,d,c >IIBb n		<IB h,r,i,d,c ? n	<IIBb h,r,i,d,c
	Trichloroethylene	<IAii h <IBii r,i,d,c >IBii n	<IA h <IB r,d		<IB h,r,i,d,c
	Vinyl chloride	<IIBb h,r,i,d,c >IIBb (n)	<IIBb (h,r,d)	<IB h,r,i,d,c ? n	

c = carcinogenic, d = developmental, h = hepatic, i = immunological, n = neurological, r = renal
BINWOE scheme was explained in Table 6. (ATSDR 2001, 2004a)
Some BINWOEs based on results from high level acute exposure studies (see detailes in Tables 7-18)
[1]**Additivity is likely at low level exposures**

Where exposure of the same individual or group of individuals to this mixture may occur for the same duration by both inhalation and oral routes, it is appropriate to sum corresponding endpoint-specific hazard indices and total cancer risks across routes to estimate aggregate hazard or risk. If an endpoint-specific aggregate hazard index exceeds one, or the aggregate cancer risks for these chemicals equals or exceeds $1x10^{-4}$, then further evaluation is needed (ATSDR 2004a), using biomedical judgment and community-specific health outcome data, and taking into account community health concerns (ATSDR 1992)

In the event of high exposure, where metabolism is saturated and the mixture components competitively inhibit each other's metabolism, a weight-of-evidence approach using the BINWOEs summarized in Table 25 could be implemented. These less-than-additive interactions on metabolism, as summarized previously, are likely to only occur at very high (100-fold or more times the corresponding MRL or TTD values) exposure levels. The BINWOEs predict that for toxicities mediated through reactive metabolites (hepatic, renal, immunological, developmental, and carcinogenic), the estimated hazard or risk is likely to be less than indicated by the endpoint-specific hazard index or the total cancer risk. For neurological effects (chloroform and trichloroethylene), the estimated hazard is likely to be greater than indicated by the hazard index for that endpoint for mixtures where chloroform is a major component (due to the

neurotoxicity of the parent compound), and indeterminate for mixtures where trichloroethylene is a major component (due to neurotoxicity of both parent compound and a metabolite).