

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

As discussed above, the mixture of chloroform, 1,1-dichloroethene, 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. Each of the four chemicals of concern cause toxic effects in two or more target organs. Three of the chemicals have been identified as likely or known carcinogenic agents (chloroform, trichloroethylene, and vinyl chloride). Separate approaches are recommended for noncancer and carcinogenic effects. All recommendations discussed below are intended to be used in consultation with the [Framework for Assessing Health Impacts of Multiple Chemical and Other Stressors](#) (ATSDR 2018).

Because suitable data, joint action models, and PBPK models are lacking for the complete mixture, the recommended approach for the exposure-based assessment of noncancer joint toxic action of this mixture for noncancer endpoints is to use the hazard index method with the target-organ toxicity dose (TTD) modification and qualitative WOE method to assess the potential consequences of dose-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 are ≥ 0.1) (Figure 1 of ATSDR 2018). 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 is ≥ 0.1 , then no further assessment of the joint toxic action is needed because dose additivity and/or interactions are unlikely to result in significant noncancer health hazard. As discussed in ATSDR (2018), 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. While the available scientific evidence suggests less-than-additive interactions among these components for most binary mixtures (with available data), interactions are only expected at very high exposure levels that saturate metabolism. Therefore, in the interest of public health protection, the recommended approach for most exposure-based assessments is assumed dose additivity.

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, respiratory, 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, 2018). 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-duration inhalation exposure are listed in Table 22, which also lists the intermediate-duration inhalation MRLs for each chemical.

Table 22. MRLs and TTDs for Intermediate-Duration Inhalation Exposure to Chemicals of Concern^a

Endpoint	Chemical			
	Chloroform (ppm)	1,1-Dichloroethene (ppm)	Trichloroethylene (ppm)	Vinyl chloride (ppm)
Hepatic	0.03	0.04	1	0.02 (intermediate-duration MRL)
Renal	0.03	0.01	1	Not applicable
Immunological	Not applicable	Not applicable	0.0004 (intermediate-duration MRL)	0.02
Respiratory	0.0008 (intermediate-duration MRL)	0.001 (intermediate-duration MRL)	Not applicable	Not applicable
Neurological	0.006	Not applicable	0.04	0.02
Developmental	0.03	0.05	0.0004 (intermediate-duration MRL)	0.5 (acute-duration MRL)

^aSee Appendices A, B, C, and D.

With the exception of chloroform, adequate chronic-duration 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-duration TTDs, and chronic-duration TTD values for chloroform were derived in Appendix A. The chronic-duration inhalation MRL for chloroform is 0.0004 ppm and the intermediate-duration inhalation

MRL is 0.0008 ppm, with both being based on similar physiological effects (i.e., respiratory tract changes). 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-duration data are lacking, the intermediate-duration inhalation TTDs and MRLs for 1,1-dichloroethene, trichloroethylene, and vinyl chloride be adjusted using a modifying factor of 3 ($10^{0.5}$) when being considered in a chronic-duration exposure scenario. The chronic-duration inhalation TTD values are presented in Table , along with the chronic-duration inhalation MRL for chloroform.

Table 23. MRLs and TTDs for Chronic-Duration Inhalation Exposure to Chemicals of Concern^a

Endpoint	Chemical			
	Chloroform (ppm)	1,1-Dichloroethene (ppm)	Trichloroethylene (ppm)	Vinyl chloride (ppm)
Hepatic	0.03	0.02	0.3	0.007
Renal	0.03	0.004	0.7	Not applicable
Immunological	Not applicable	Not applicable	0.0004 (chronic-duration MRL)	0.02
Respiratory	0.0004 (chronic-duration MRL)	0.001 (chronic-duration MRL)	Not applicable	Not applicable
Neurological	0.006	Not applicable	0.01	0.02
Developmental	0.03	0.02	0.0004 (chronic-duration MRL)	0.2

^aSee 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, 2018), and are listed, along with MRLs, in Table 24 for intermediate-duration exposure and Table 25 for chronic-duration exposure.

Table 24. MRLs and TTDs for Intermediate-Duration Oral Exposure to Chemicals of Concern^a

Endpoint	Chemical			
	Chloroform (mg/kg/day)	1,1-Dichloroethene (mg/kg/day)	Trichloroethylene (mg/kg/day)	Vinyl chloride (mg/kg/day)
Hepatic	0.1 (intermediate- duration MRL)	0.3	0.7	0.003
Renal	0.1	0.3	2	Not applicable
Immunological	Not applicable	Not applicable	0.0005 (intermediate- duration MRL)	Insufficient data
Neurological	0.1	Not applicable	0.0005	0.04
Developmental	0.1	0.3	0.0005 (intermediate- duration MRL)	Insufficient data

^aSee Appendices A, B, C, and D.

Table 25. MRLs and TTDs for Chronic-Duration Oral Exposure to Chemicals of Concern^a

Endpoint	Chemical			
	Chloroform (mg/kg/day)	1,1-Dichloroethene (mg/kg/day)	Trichloroethylene (mg/kg/day)	Vinyl chloride (mg/kg/day)
Hepatic	0.02 (chronic-duration MRL)	0.05 (chronic-duration MRL)	0.7	0.003 (chronic-duration MRL)
Renal	0.1	0.05	0.4	Not applicable
Immunological	Not applicable	Not applicable	0.0005 (chronic- duration MRL)	Insufficient data
Neurological	0.02	Not applicable	0.0005	0.04
Developmental	0.02	0.05	0.0005 (chronic- duration MRL)	Insufficient data

^aSee 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 22, 23, 24, and 25, or newer values as they become available. The hazard index is unitless so the exposure and guidance values must be in the same units (e.g., ppm). 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_{CHCl_3} is the intermediate-duration inhalation exposure to chloroform (in ppm), MRL_{CHCl_3} is the intermediate-duration inhalation MRL for chloroform (based on hepatic effects, in ppm), E_{DCE} is the intermediate-duration inhalation exposure to 1,1-dichloroethene (in ppm), MRL_{DCE} is the intermediate-duration inhalation MRL for 1,1-dichloroethene (based on hepatic effects, in ppm), E_{TCE} is the intermediate-duration inhalation exposure to tetrachloroethylene (in ppm), $TTD_{TCE,HEPATIC}$ is the intermediate-duration inhalation TTD for hepatic effects of trichloroethylene (in ppm), E_{VC} is the intermediate-duration inhalation exposure to vinyl chloride (in ppm), and MRL_{VC} the intermediate-duration inhalation MRL for vinyl chloride (based on hepatic effects, in ppm). The process can be then repeated for each endpoint of concern for intermediate-duration 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-duration inhalation exposure, using chronic-duration exposure concentrations and chronic-duration inhalation TTDs and MRLs, and for intermediate- and chronic-duration oral exposure, for which the exposures are estimated as oral intakes in mg/kg/day, consistent with the units of the intermediate- and chronic-duration oral MRLs and TTDs. Components for which data are not available, and therefore no TTD can be derived, or which do not affect the endpoint are not included in the endpoint-specific hazard index calculations.

If the hazard index for effects on a noncancer endpoint of concern for any duration and route is >1 , it provides preliminary evidence that the mixture may constitute a health hazard due to the joint toxic action of components on that endpoint (ATSDR 2018). The impact of interactions from the WOE analysis also is considered. For this particular mixture, the available data and pharmacokinetic models on the component pairs support less-than-additive interactions for the individual pairs for most endpoints attributed to reactive metabolites, as shown in Table 26; for neurological effects of chloroform, the available mechanisms suggest greater-than-additive interactions, and for the neurological effects of trichloroethylene and vinyl chloride, the direction of interaction is indeterminate. However, since the mechanism behind those interactions is likely to only occur at very high (e.g., ≥ 100 -fold 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.

Table 26. Matrix of BINWOE Determinations for Simultaneous Exposure to High Levels of Chemicals of Concern^a

		ON THE TOXICITY OF			
		Chloroform	1,1-Dichloroethene	Trichloroethylene	Vinyl chloride
EFFECT OF	Chloroform		<IIBb h,rn,rs,d	<IAii h <IBii rn,i,d,c ? n	<IIBb h,i,d,c ? n
	1,1-Dichloroethene	<IIBb h,rn,rs,d,c >IIBb n		<IB h,rn,i,d,c ? n	<IIBb h,r,i,d,c ? n
	Trichloroethylene	<IAii h <IBii rn,rs,d,c >IBii n	<IA h <IB rn,rs,d		<IB h,r,i,d,c ? n
	Vinyl chloride	<IIBb h,rn,rs,d,c >IIBb n	<IIBb h,rn,rs,d	<IB h,rn,i,d,c ? n	

^aBINWOE scheme was explained in Table 7 (ATSDR 2001, 2018). Some BINWOEs are based on results from high-level, acute-duration exposure studies (see details in Tables 8–19). Additivity is likely at low-level exposures; dose additivity is assumed for noncancer effects and response additivity is assumed for carcinogenic effects.

c = carcinogenic; d = developmental; h = hepatic; i = immunological; n = neurological; rn = renal; rs = respiratory; ? = not known

The default cancer risk assessment 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, which is a good approximation of response addition for low component 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 is $\geq 1 \times 10^{-6}$, then no further assessment of joint toxic action is needed due to the low likelihood that additivity and/or interactions would result in a significantly enhanced 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 for chloroform, trichloroethylene, and vinyl chloride.

If this screening procedure indicates preliminary evidence of a mixtures health hazard, additional evaluation is needed to assess whether a public health hazard exists (ATSDR 2018). The additional evaluation includes biomedical judgment, assessment of community-specific health outcome data, and consideration of community health concerns (ATSDR 1992).

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 is >1 , or the aggregate cancer risks for these chemicals is $\geq 1 \times 10^{-4}$, then further evaluation is needed (ATSDR 2018), using biomedical judgment and community-specific health outcome data, and considering community health concerns (ATSDR 1992).

In the event of high exposure, where metabolism is saturated and the mixture components competitively inhibit each other's metabolism, a WOE approach using the BINWOEs summarized in Table 26 could be implemented. These predicted interactions based on metabolic saturation, as summarized previously, are likely to only occur at very high (e.g., ≥ 100 -fold times the corresponding MRL or TTD values) exposure levels. The BINWOEs predict that for toxicities mediated through reactive metabolites (hepatic, renal, immunological, respiratory, 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, trichloroethylene, and vinyl chloride), 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) or where vinyl chloride is a major component (due to lack of mechanistic understanding). Due to the number of compounds metabolized via cytochrome P450 enzymes, there is also potential for other co-exposures to impact the toxicity of this mixture at high concentrations that saturate metabolism (e.g., other chlorinated hydrocarbons), inhibit microsomal mixed-function oxidases (MFOs) (e.g., carbamates), or induce microsomal MFOs (e.g., acetone) (ATSDR 2019, 2022c, 2024a, 2024b).