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

As discussed above, the mixture of carbon monoxide, formaldehyde, methylene chloride, nitrogen dioxide, and tetrachloroethylene was chosen as the subject for this interaction profile because they are airborne compounds that are commonly found in the home environment. The exposure scenarios of greatest concern are likely to be inhalation exposures of 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 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 2004). 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 has 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 (1992, 2004), the exposure-based assessment of 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 endpoint-specific (target-organ-specific) hazard indexes for the endpoints of concern for a particular mixture. The endpoints of concern for this mixture are hematological, cardiovascular, neurological, respiratory, and hepatic effects. Therefore, these endpoints are candidates for TTD development for the components of this mixture. TTDs were not derived for endpoints that are sensitive endpoints for only one component of the mixture. The TTDs were derived as described in the Appendices to this document, using the methods recommended by ATSDR (2001, 2004). The derived values are listed in Table 17, which also lists the chronic inhalation MRLs or other guidance values. BINWOEs have been developed for these endpoints also, as presented in Section 2.3, and summarized later in Section 3.

Table 17. MRLs and TTDs for Inhalation Exposure to Chemicals of Concern[a]

Endpoint	Chemical				
	Carbon Monoxide	Formaldehyde	Methylene Chloride	Nitrogen Dioxide	Tetrachloro-ethylene
Hematological	1 ppm (acute TTD)	NA	0.3 ppm (chronic MRL)	NA	NA
Cardiovascular	1 ppm (acute TTD)	NA	NA	NA	NA
Neurological	3 ppm (acute TTD)	NA	0.6 ppm (acute MRL)	NA	0.04 ppm (chronic MRL)
Respiratory	NA	0.008 ppm (chronic MRL)	50 ppm	0.08 ppm (acute TTD)	NA
Hepatic	NA	NA	0.3 ppm (intermediate MRL)	NA	0.1 ppm

[a]See Appendices A, B, C, D, and E
NA = Not Applicable

The hazard index is calculated using the guidance values for the effect of concern, shown in Table 17, or newer values as they become available. This process is shown, using neurological effects as an example, in the following equation:

$$HI_{NEURO} = \frac{E_{CO}}{TTD_{CO\,NEURO}} + \frac{E_{MeCl}}{MRL_{MeCl}} + \frac{E_{TCEt}}{MRL_{TCEt}}$$

where HI_{NEURO} is the hazard index for neurologic toxicity, E_{CO} is the exposure to carbon monoxide, $TTD_{CO\,NEURO}$ is the TTD_{NEURO} for carbon monoxide (in ppm), E_{MeCl} is the exposure to methylene chloride, MRL_{MeCl} is the acute inhalation MRL for methylene chloride (based on neurologic effects, in ppm), E_{TCEt} is the exposure to tetrachloroethylene (in ppm), and MRL_{TCEt} is the chronic inhalation MRL for tetrachloroethylene. The process can be then repeated for each endpoint of concern, using the appropriate exposure concentrations and TTDs/MRLs, resulting in endpoint-specific hazard indices for each effect of concern for the mixture. Components for which data are not available, and therefore no TTD can be derived, are not included in the endpoint-specific hazard index calculation.

If the hazard index for effects on an endpoint of concern exceeds 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 2004). The impact of interactions from the WOE analysis also is considered; however, since the

available data do not indicate non-additive actions for any of the component pairs, the impact of the WOE analysis will be less than the case of some other mixtures.

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 2004). 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 would involve calculating the carcinogenic risk for each component by multiplying lifetime inhalation exposure estimates for each component by the appropriate EPA cancer inhalation unit risk (an estimate of cancer risk per unit of exposure). If only one or if none of the component risks equals or exceeds $1x10^{-6}$, then no further assessment of joint toxic action would be needed due to the low likelihood that additivity and/or interactions would result in a significant health hazard. For this particular mixture, only formaldehyde and methylene chloride have unit risk values, so the focus on carcinogenic risks will lie primarily on those compounds. As noted in section 2.2.2 (Tables 9 and 10), the available weight of evidence indicates an additive interaction with regard to carcinogenic effects for methylene chloride and formaldehyde.

Table 18. Matrix of BINWOE Determinations for Intermediate or Chronic Simultaneous Exposure to Chemicals of Concern

EFFECT OF	ON THE TOXICITY OF: Carbon Monoxide	Formaldehyde	Methylene Chloride	Nitrogen Dioxide	Tetrachloro-ethylene
Carbon Monoxide		?	=IA2 h,n ? r, c	?	?
Formaldehyde	?		=IB1 c =IIC1 r ? h,n	=IIIC2 r ? i	?
Methylene Chloride	=IA2 h =IIB2 n,v,d	=IB1 r,c		?	?
Nitrogen Dioxide	?	=IIIC2 r ? c	?		?
Tetrachloroethylene	?	?	?	?	

r = respiratory, n = neurological, h = hematological, c = carcinogenic, v=cardiovascular, d=developmental, i=immunological

The BINWOE determinations were explained in Section 2.3.; for classification see Table 4.

BINWOE scheme (with numerical weights in parentheses) condensed from ATSDR (2001, 2004):