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. Two or more noncancer targets of toxicity have been identified in each of the five chemicals of concern. Three of the chemicals have been identified as likely or known carcinogenic agents (formaldehyde, methylene chloride, and tetrachloroethylene). 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 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-based guidance values, such as MRLs. If only one compound, or if none of the compounds, has 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 a significant noncancer health hazard. As discussed by ATSDR (1992, 2018), 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, neurological, respiratory, hepatic, and developmental 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, 2018). The derived values are listed in Table 18, which also lists the intermediate- and

chronic-duration inhalation MRLs or other health-based guidance values. BINWOEs have been developed for these endpoints also, as presented in Section 2.3, and summarized later in Section 3.

Table 18. MRLs and TTDs for Inhalation Exposure to Chemicals of Concern[a]

	Chemical				
Endpoint	Carbon monoxide	Formaldehyde	Methylene chloride	Nitrogen dioxide	Tetrachloroethylene
Hematological	1 ppm (intermediate- and chronic-duration TTD)	NA	0.3 ppm (intermediate- and chronic-duration TTD)	NA	NA
Neurological	4 ppm (intermediate- and chronic-duration TTD)	NA	0.6 ppm (intermediate- and chronic-duration TTD)[b]	NA	0.006 ppm (intermediate- and chronic-duration MRLs)
Respiratory	NA	0.03 ppm (intermediate-duration MRL) 0.008 ppm (chronic-duration MRL)	2 ppm (intermediate- and chronic-duration TTD)	0.03 ppm (intermediate- and chronic-duration TTD)	NA
Hepatic	NA	NA	0.3 ppm (intermediate-and chronic-duration MRLs)	NA	0.03 ppm (intermediate- and chronic-duration TTD)
Developmental	1 ppm (intermediate- and chronic-duration TTD)	0.2 ppm (intermediate- and chronic-duration TTD)	NA	NA	NA

[a]See Appendices A, B, C, D, and E for details on derivations of TTDs.
[b]The acute-duration MRL for methylene chloride was adopted as the TTD_{NEURO} values for methylene chloride; see Appendix C for details.

MRL = Minimal Risk Level; NA = not applicable; TTD = target-organ toxicity dose

The hazard index is calculated using the health-based guidance values for the effect of concern, shown in Table 18, or newer values as they become available, where the exposure route and duration of the exposure and health-based guidance values should match the route and duration for which the hazard index is developed. 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 neurological effects following chronic-duration inhalation exposure 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 chronic-duration inhalation neurological toxicity, E_{CO} is the exposure to carbon monoxide, $TTD_{CO\,NEURO}$ is the chronic-duration TTD_{NEURO} for carbon monoxide (in ppm), E_{MeCl} is the exposure to methylene chloride, MRL_{MeCl} is the acute-duration inhalation MRL for methylene chloride (based on neurological effects, in ppm, which was adopted as the chronic-duration TTD_{NEURO} for methylene chloride), E_{TCEt} is the exposure to tetrachloroethylene (in ppm), and MRL_{TCEt} is the chronic-duration inhalation MRL for tetrachloroethylene (based on neurological effects, in ppm). The same process can be then repeated for each endpoint and duration 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, or which do not affect the endpoint are not included in the endpoint-specific hazard index calculation.

If the hazard index for effects on a noncancer endpoint of concern for any duration 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 was 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 in the case of some other mixtures.

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 inhalation carcinogenic risk for each component is calculated 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 inhalation exposure). If only one or if none of the component risks is $\geq 1 \times 10^{-6}$, 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 significantly enhanced health hazard. For this particular mixture, formaldehyde, methylene chloride, and tetrachloroethylene 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 WOE indicates an additive joint action with regard to carcinogenic effects for methylene chloride and formaldehyde.

If this screening procedure indicates preliminary evidence of a mixture exposure 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).