4. Conclusions

This interaction profile recommends the use of component-based approaches that assume additive joint toxic action in exposure-based assessments of possible noncancer or cancer health hazards from inhalation exposure to mixtures of carbon monoxide, formaldehyde, methylene chloride, nitrogen dioxide, and tetrachloroethylene. This recommendation is based on the following factors: (1) there are no direct data available to characterize health hazards (and dose-response relationships) from mixtures containing all five components; (2) PBPK/PD models have not yet been developed that would predict pertinent target doses of the components under scenarios involving exposure to mixtures of all five components; and (3) available information on toxic actions of the individual components indicates that joint actions of carbon monoxide, formaldehyde, methylene chloride, nitrogen dioxide, and tetrachloroethylene on several toxicity targets are plausible, including hematological effects, respiratory effects, neurological alterations, hepatic injury, developmental effects, and cancer. With data on the individual components suggesting possible sites of joint toxic action, but no data available on the toxicity or behavior of the complete mixture or the relevant submixtures, a default component-based approach assuming additivity was therefore recommended. Data evaluating the complete mixture *in vivo*, *in vitro*, or via computational modeling may provide relevant data to inform future recommendations.

WOE analyses of available data on the joint toxic action of mixtures of these components indicate that scientific evidence for greater-than-additive or less-than-additive interactions among these components is limited, with the majority of limited available interaction data suggesting additive joint toxicity. Data are inadequate to characterize the possible modes of joint action on most of the pertinent toxicity targets. Therefore, it is recommended that dose additivity should generally be assumed as a public health protective measure in exposure-based assessments of noncancer health hazards from exposure to mixtures of these components. The dose additivity approach to screening for potential noncancer health hazards involves the estimation of endpoint-specific hazard indexes using MRLs from the toxicological profiles and TTDs derived in this interaction profile. This approach is appropriate when the hazard quotients of at least two of the components are ≥0.1 (ATSDR 2018). Potential cancer risk is estimated by adding the chemical-specific risks for formaldehyde, methylene chloride, and tetrachloroethylene.

Endpoint-specific hazard indices (e.g., hazard indices for hepatic effects) or cancer risks for the same duration (e.g., chronic) can be summed across routes to estimate the aggregate health hazard or risk, if it is likely that the same individual or group of individuals would be exposed by both routes. If an endpoint-specific hazard index is >1, or the total cancer risk 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 taking into account community health concerns (ATSDR 1992). For very high exposures, interactions may occur (e.g., ≥100-fold above the MRLs or TTDs), and their potential impact can be determined using the WOE results, as summarized above.