1. Introduction

The primary purpose of this *Interaction Profile for Carbon Monoxide, Formaldehyde, Methylene Chloride, Nitrogen Dioxide, and Tetrachloroethylene* is to evaluate data on the toxicology of the "whole" mixture and the joint toxic action of the chemicals in the mixture in order to recommend approaches for assessing the potential hazard of this mixture to public health. To this end, the profile evaluates the whole mixture data (if available), focusing on the identification of health effects of concern, and adequacy and relevance of physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) models for the mixture. The profile also evaluates the evidence for joint toxic action—additivity and interactions—among the mixture components. A weight-of-evidence (WOE) approach is commonly used in these profiles to evaluate the influence of interactions in the overall toxicity of the mixture. The WOE evaluations are qualitative in nature, although the Agency for Toxic Substances and Disease Registry (ATSDR) recognizes that observations of toxicological interactions depend greatly on exposure doses and that some interactions appear to have thresholds. Thus, the interactions are evaluated in a qualitative manner to provide a sense of what influence the interactions may have when they do occur. The profile provides environmental health scientists with ATSDR Office of Innovation and Analytics, Toxicology Section recommended approaches for the incorporation of the whole mixture data or the concerns for additivity and interactions into an assessment of the potential hazard of this mixture to public health. These approaches can then be used with specific exposure data from hazardous waste sites or other exposure scenarios. For more information on different approaches to evaluating mixtures and background information on chemical interactions, readers can refer to the *Framework for Assessing Health Impacts of Multiple Chemical and Other Stressors* (ATSDR 2018).

The carbon monoxide, formaldehyde, methylene chloride, nitrogen dioxide, and tetrachloroethylene mixture was chosen as the subject for this interaction profile based primarily on concerns regarding co-exposure to these chemicals in residential indoor air. All of the components of the mixture are commonly found in the indoor air environment of the home, as described briefly below. Concentrations of these chemicals commonly are higher in indoor air than in outdoor air (Table 1). Since this mixture is common in residential air, understanding potential interactions will be useful for risk characterization in homes, including those near hazardous waste sites. Because they are all highly volatile, the focus of the interaction profile will be on inhalation exposure, with an emphasis on intermediate- and chronic-duration effects.

Table 1. Indoor Air Quality—Levels of Pollutants in Households

Chemical	Exposure level	Exposure scenario
Carbon monoxide	0.5–5 ppm	Homes without gas stoves
	5–15 ppm	Near properly adjusted gas stoves
	>30 ppm	Near poorly adjusted gas stoves
Formaldehyde	<0.1 ppm	Older homes without urea-formaldehyde foam insulation
	>0.3 ppm	Homes with significant amount of new pressed wood products
Nitrogen dioxide	< outdoor levels (by ½)	Homes without combustion appliances
	> outdoor levels	Homes with gas stoves, kerosene heaters, un-vented gas space heaters, etc.
Volatile organic compounds (including methylene chloride and tetrachloroethylene)	2–5 times	Levels inside homes higher compared to outside air regardless of whether the homes are located in rural or highly industrialized area
	1,000 times	During and after certain activities, such as paint stripping, levels higher than background outdoor levels

Source: EPA (2024a, 2024b, 2024c, 2025)

Carbon monoxide is a colorless, odorless gas that is formed as a product of incomplete combustion. Numerous incidents of elevated carbon monoxide levels in the home have been reported, with the primary sources being faulty ventilation of furnaces or fireplaces. Carbon monoxide's toxic effects stem from its binding with the ferrous iron in hemoglobin, resulting in the formation of carboxyhemoglobin (COHb). COHb is unable to bind molecular oxygen, resulting in diminished oxygen-carrying capacity of the blood. Effects of carbon monoxide exposure include headache, nausea, chest pain during exercise, and, at high exposure levels, convulsions, coma, and death. Developmental effects can result from maternal/fetal hypoxia. There is also evidence of cardiovascular disease following repeated exposure to low levels of carbon monoxide. More information on carbon monoxide is found in Appendix A.

Formaldehyde is a colorless gas at room temperature. Sources of formaldehyde exposure within the home include cigarettes and other tobacco products, gas cookers, and open fireplaces. Formaldehyde is found in many products used every day around the house, such as antiseptics, medicines, cosmetics, dishwashing liquids, fabric softeners, shoe-care agents, carpet cleaners, glues and adhesives, lacquers, paper, and plastics, and some types of wood products. It is also used as a preservative in some foods, such as some types of Italian cheeses, dried foods, and fish. It has a pungent, distinct odor and may cause a burning sensation to the eyes, nose, and lungs at high concentrations and damage to the respiratory tissues. There is also some evidence of reproductive or developmental toxicity. The Department of Health and Human Services (HHS) has categorized formaldehyde as a *known to be a human carcinogen*

based on sufficient evidence of carcinogenicity in humans (NTP 2021a). The U.S. Environmental Protection Program (EPA) classifies formaldehyde as *carcinogenic to humans* (EPA 2024d). The International Agency for Research on Cancer (IARC) classifies formaldehyde as *carcinogenic to humans* (Group 1) based on sufficient evidence in humans and experimental animals (IARC 2012). More information on formaldehyde is found in Appendix B and ATSDR (1999).

Methylene chloride, also known as dichloromethane, is a colorless liquid that has a mild sweet odor, evaporates easily, and does not burn easily. It is widely used as an industrial solvent and as a paint stripper. It can also be found in certain aerosol and pesticide products, some spray paints, automotive cleaners, and other household products. Methylene chloride is used in the manufacture of photographic film. Methylene chloride is metabolized in the body to both carbon monoxide and formaldehyde, and may result in COHb formation, compensatory hematopoiesis, damage to respiratory tissues, hepatic effects, and neurological effects, including headache, dizziness, intoxication, and incoordination. HHS (NTP 2021b) has categorized methylene chloride as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals. The EPA (2011a) classifies methylene chloride (dichloromethane) as *likely to be carcinogenic to humans* based on inadequate human data and sufficient evidence of carcinogenicity in animals. IARC (2016) classified methylene chloride (dichloromethane) as *probably carcinogenic to humans* (Group 2A) based on limited evidence in humans and sufficient evidence in experimental animals. More information on methylene chloride can be found in Appendix C and ATSDR (2000).

Nitrogen dioxide is a colorless gas that may be found at high levels in both the indoor and outdoor environment. Within the home, concentrations of nitrogen oxides, including nitrogen dioxide, may be elevated when unvented combustion appliances are used for cooking or heating (e.g., poorly vented fireplaces or furnaces). The primary effects of inhaled nitrogen dioxide involve irritation of the respiratory tract, with high-level exposures also resulting in small deficits to the immune system, particularly in the lungs. Exposure has also been associated with cardiovascular, neurological, and developmental effects. More information on nitrogen dioxide can be found in Appendix D.

Tetrachloroethylene is a synthetic chemical that is widely used for drycleaning of fabrics and for metal-degreasing operations. It is a nonflammable liquid at room temperature but evaporates easily into the air. It may be found in the home environment as a result of drycleaning operations or when one or more of the members of the household work in processes involving tetrachloroethylene. Tetrachloroethylene has a sharp, sweet odor; most people can smell tetrachloroethylene at levels ≥1 ppm. The primary effects of

tetrachloroethylene are neurological, including decreased performance, headache, dizziness, and drowsiness. Other effects of tetrachloroethylene include renal and hepatic effects. Tetrachloroethylene is classified as *reasonably anticipated to be a human carcinogen* by HHS (NTP 2021c) based on evidence in experimental animals. Tetrachloroethylene is classified as *likely to be carcinogenic to humans* by the EPA (2012) based on suggestive evidence in humans and conclusive evidence in animals. Based on evidence in experimental animals, IARC (2014) classified tetrachloroethylene as *probably carcinogenic to humans* (Group 2A). More information on tetrachloroethylene can be found in Appendix E and ATSDR (2019).

Before evaluating the relevance of joint toxic action data for these chemicals, some understanding of endpoints of concern for inhalation exposure to this mixture is needed. The endpoints of concern include the critical effects that are the bases for Minimal Risk Levels (MRLs) or other health-based guidance values, and any other endpoints that may become significant because they are shared targets of toxicity or due to interactions (ATSDR 2018).

Carbon monoxide's critical effect is the formation of COHb, which is a hematological effect. ATSDR (2012) has not derived MRLs and EPA has not derived a reference concentration (RfC) for carbon monoxide. Increased blood COHb caused by carbon monoxide exposure may also lead to cardiovascular, neurological, or developmental effects.

The critical effect for formaldehyde inhalation, and the basis for ATSDR's inhalation MRLs and EPA's RfC, is respiratory system toxicity, specifically irritant effects in humans (ATSDR 1999; EPA 2024d). EPA (2024d) derived an inhalation unit risk for cancer of 1.1×10^{-5} per $\mu g/m^3$ for formaldehyde.

Several different endpoints are sensitive effects of methylene chloride inhalation. ATSDR's acute-duration inhalation MRL is based on neurological effects, the intermediate-duration inhalation MRL is based on hepatic effects, and the chronic-duration inhalation MRL is based on hematologic effects (ATSDR 2000). EPA's RfC for methylene chloride is based on hepatic effects (EPA 2011a). Methylene chloride exposure may also result in respiratory effects. EPA (2011a) derived an inhalation unit risk for cancer of 1×10^{-8} per $\mu g/m^3$ for methylene chloride.

The primary effect of nitrogen dioxide inhalation is injury to the respiratory tract, which is believed to be the result of the reactive nature of nitrogen dioxide. ATSDR has not derived MRLs and EPA has not

derived an RfC for nitrogen dioxide. Nitrogen dioxide may also cause immunological deficits at high doses.

The most sensitive effects of tetrachlorethylene inhalation are neurological, including decreased reaction times, headache, dizziness, and drowsiness. ATSDR's chronic-duration inhalation MRL and EPA's RfC for tetrachloroethylene are based on neurological effects in exposed humans (ATSDR 2019; EPA 2012). Other sensitive endpoints of tetrachloroethylene include hepatic and renal effects. EPA (2011a) derived an inhalation unit risk for cancer of $2.6x10^{-7}$ per $\mu g/m^3$ for tetrachloroethylene.

The basis for the MRLs or other guidance values for these five chemicals, as well as other sensitive effects, are summarized in Table 2. As can be seen, while there is no single endpoint that is a sensitive effect of all components of the mixture, there are several endpoints that are of concern for two or more chemicals in the mixture; those endpoints are the focus of the component-based mixture assessments in Chapters 2 and 3. No pertinent studies of the toxicity or interactions of, or of PBPK models for the complete mixture, or any of the quaternary or tertiary submixtures were located. Only limited toxicological data are available for the individual component binary mixtures. ATSDR toxicological profiles for formaldehyde (ATSDR 2010), methylene chloride (ATSDR 2000), carbon monoxide (ATSDR 2012), and tetrachloroethylene (ATSDR 2019); the EPA Integrated Risk Information System (IRIS) assessment for formaldehyde (EPA 2024d), the ATSDR systematic evidence map (SEM) for methylene chloride (ATSDR 2022), and literature reviews and meta-analyses for carbon monoxide and nitrogen dioxide are the primary source of information presented in the appendices concerning the toxicokinetics, health effects, mechanisms of action, and health-based guidance values for these chemicals.

Table 2. Potential Health Effects of Concern for Intermediate- and Chronic-Duration Inhalation Exposure to the Mixture Carbon Monoxide, Formaldehyde, Methylene Chloride, Nitrogen Dioxide, and Tetrachloroethylene[a,b]

Endpoint	Carbon monoxide	Formaldehyde	Methylene chloride	Nitrogen dioxide	Tetrachloro-ethylene
Hematological	X		**X**		
Cardiovascular	X				
Neurological	X		**X**		**X**
Respiratory		**X**	X	X	
Hepatic			**X**		X
Renal					X
Developmental	X	X			
Immunological				X	
Cancer		X	X		X

[a]See Appendices A, B, C, D, and E for additional information on health-based guidance values and health effects.
[b]The basis for the MRLs or health assessment approaches are bolded (no MRLs have been set for carbon monoxide or nitrogen dioxide); other sensitive effects are listed in regular typeface.