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, adequacy of the data as the basis for a mixture Minimal Risk Level (MRL), 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 weight-of-evidence 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 Division of Toxicology and Environmental Medicine's (DTEM) 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.

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 the 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). 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 UFFI
	>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.
VOCs	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

UFFI = urea-formaldehyde foam insulation; VOCs = volatile organic compounds (including methylene chloride, tetrachloroethylene)

Source: US Environmental Protection Agency (2007) at www.epa.gov/iaq/

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). Carboxyhemoglobin 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. 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, dish-washing 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. IRIS (U.S. EPA 2005) presently classifies formaldehyde in carcinogenicity group B1 (probable human carcinogen). The inhalation unit risk for formaldehyde is 1.3E-5 $(ug/m^3)^{-1}$. 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 carboxyhemoglobin formation, damage to respiratory tissues, and neurological effects, including headache, dizziness, intoxication, and incoordination. EPA (IRIS 2004) presently classifies dichloromethane as group B2 (probable human carcinogen), based on inadequate human data and sufficient evidence of carcinogenicity in animals; the inhalation unit risk is 4.7E-7 per $\mu g/m^3$. More information on methylene chloride can be found in Appendix C and ATDSR (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 NO_2, 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 NO_2 involve irritation of the respiratory tract, with high-level exposures also resulting in small deficits to the immune system, particularly in the lungs. More information on NO_2 can be found in Appendix D.

Tetrachloroethylene is a synthetic chemical that is widely used for dry cleaning 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 dry cleaning operations, or when one or more of the members of the household works in processes involving tetrachloroethylene. Tetrachloroethylene has a sharp, sweet odor; most people can smell tetrachloroethylene at levels of 1 ppm or more. The primary effects of tetrachloroethylene are neurological, including decreased performance, headache, dizziness, and drowsiness. Other effects of tetrachloroethylene include renal and hepatic effects and, at very high doses, cardiovascular effects. Tetrachloroethylene is currently under review by the EPA IRIS program and will be a component of the upcoming NRC review regarding its carcinogenicity. More information on tetrachloroethylene can be found in Appendix E and ATSDR (1997).

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 MRLs or other health guidance values, and any other endpoints that may become significant because they are shared targets of toxicity or due to interactions (ATSDR 2004).

Carbon monoxide's critical effect is the formation of carboxyhemoglobin, which is a hematological effect. ATSDR has not derived MRLs and EPA has not derived an RfC for carbon monoxide. Increased blood carboxyhemoglobin 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 effects on the respiratory system, specifically irritant effects in humans. IRIS (U.S. EPA 2005) presently classifies formaldehyde in carcinogenicity group B1 (probable human carcinogen), with an inhalation unit risk of 1.3E-5 $(ug/m^3)^{-1}$.

Several different endpoints are sensitive effects of methylene chloride inhalation. ATSDR's acute inhalation MRL is based on neurological effects, the intermediate inhalation MRL is based on hepatic effects, and the chronic inhalation MRL is based on hematologic effects. EPA's RfC for methylene chloride is based on hepatic effects. Methylene chloride exposure may also result in respiratory effects. EPA (IRIS 2004) presently classifies dichloromethane as group B2 (probable human carcinogen), with an inhalation unit risk of 4.7E-7 per $\mu g/m^3$.

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 NO_2. ATSDR has not derived MRLs and EPA has not derived an RfC for NO_2. 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 for tetrachloroethylene is based on neurological effects in exposed humans. EPA has not derived an RfC for tetrachloroethylene. Other sensitive endpoints of tetrachloroethylene include cardiovascular, hepatic, and renal effects.

The bases for the MRLs or other guidance values, 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. 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. Relatively recent ATSDR toxicological profiles are available for formaldehyde (ATSDR 1999), methylene chloride (ATSDR 2000), and tetrachloroethylene (ATSDR 1997); these documents are the primary source of information presented in the Appendices concerning the toxicokinetics, health effects, mechanisms of action, and health guidelines for these chemicals.

Table 2. Potential Health Effects of Concern for Intermediate and Chronic Inhalation Exposure to the Mixture Carbon Monoxide, Formaldehyde, Methylene Chloride, Nitrogen Dioxide, and Tetrachloroethylene (See Appendices A, B, C, D, and E)

Endpoint	Carbon Monoxide	Formaldehyde	Methylene Chloride	Nitrogen Dioxide	Tetrachloro-ethylene
Hematological	X		**X**		
Cardiovascular	X				X
Neurological	X		**X**		**X**
Respiratory		**X**	X	X	
Hepatic			**X**		X
Renal					X
Developmental	X				
Immunological				X	
Cancer		X	X		

The basis for the MRL or health assessment approach is bolded; other sensitive effects are listed in regular typeface.