ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR METHYLENE CHLORIDE

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CONTENTS

ADDENDUM for Methylene Chloride
Supplement to the 2000 Toxicological Profile for Methylene Chloride

Background Statement

This addendum to the Toxicological Profile for Methylene Chloride supplements the profile that was released in 2000.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986, which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances and that the profiles be revised "no less often than once every three years." CERCLA further states that the Administrator will "establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" [Title 42, Chapter 103, Subchapter I, § 9604 (i)(1)(B)].

The purpose of this addendum is to provide to the public and other federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature since the release of the profile in 2000.

Chapter numbers in this addendum coincide with the Toxicological Profile for Methylene Chloride (2000). This document should be used in conjunction with the profile. It does not replace it.

2. HEALTH EFFECTS

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

2.2.1 Inhalation Exposure

2.2.1.1 Death

An eighteen-year-old male working in a furniture stripping shop died after inhaling methylene chloride vapors (levels not reported) and collapsing into a stripping tank (Estill et al. 2002).

Goldberg and Theriault (1994) conducted a retrospective cohort mortality study of workers at a Canadian synthetic textiles plant in Drummondville, Quebec. Mortality rates for most causes of death were less than expected. There was limited evidence for an association of liver and gallbladder cancers with employment in the cellulose acetate fiber manufacturing unit. However, methylene chloride had limited use at this plant. It was used with only 2 of 30 cellulose triacetate extrusion machines for two years, and it was used in the closed-circuit cooling systems of the cellulose acetate acetylization vessels in the unit that fabricated cellulose acetate. Thus, the authors concluded that methylene chloride exposure was unlikely to account for the observed increases in mortality from liver and gallbladder cancer in this unit.

2.2.1.8 Cancer

Blair et al. (1998) evaluated mortality and cancer rates in a cohort study of civilian aircraft maintenance workers (10,730 men and 3,727 women) employed at least one year between 1952 and 1956 and compared these with rates for the state of Utah. Workers exposed to methylene chloride showed elevated incidences of mortality from non-Hodgkin's lymphoma (relative risk [RR] 3.0; 95% CI 0.9–10.0), multiple myeloma (RR 3.4; 95% CI 0.9–13.2), and breast cancer among women (RR 3.0; 95% CI 1.0–8.8). However, because workers had the potential for exposure to many chemicals, the overlap of exposures limited the ability to evaluate disease risks from exposure to individual chemicals in this study. None-the-less, mortality rates from all

causes and cancer rates for all cancers were slightly lower than rates for the state of Utah.

Shannon et al. (1988) conducted a retrospective cohort mortality study of Canadian lamp-manufacturing workers. The study included 826 men and 1,044 women employed between 1960 and 1975. Of these workers, 46 men and 203 women had worked in the coiling and wire-drawing area (CWD) where methylene chloride was used. Among women, a two-fold increase in breast cancer was found in the CWD cohort (SMR 2.04; 95% CI 0.88–4.02), but not elsewhere in the plant. The excess was greatest in those who had worked more than five years in the CWD. Although methylene chloride had been used in this area, no direct measures of exposure were available, and possible exposures to other chemicals increased the potential for confounding.

The metabolism of methylene chloride to formaldehyde via glutathione-S-transferase (GST) enzymes (specifically GSTT1) has been linked to increased cancer risk. Since the role of GST enzymes in estimating the risk of methylene chloride to humans is complicated by genetic polymorphism in the GSTT1 gene, El-Masri et al. (1999) investigated the effect of incorporating information on the genetic polymorphism of GSTT1 into a model of the risk distribution of methylene chloride in a human population. Their method used Monte Carlo simulation and physiologically based pharmacokinetic (PBPK) modeling combined with available information of ethnic distributions and polymorphism variability within each ethnic group of the population. The PBPK model used was based on earlier models, and it estimated the amount of DNA-protein cross links (DPX) caused by metabolism of methylene chloride (as the surrogate for cancer risk estimates). Their results showed that for a 6 hour/day exposure to methylene chloride, average and median risk estimates were approximately 30% lower when GSTT1 polymorphisms were included (since these polymorphisms are protective). In a sample of 1000 randomly selected individual from the U.S. population, mean lifetime risk estimates from exposure to 1 ppm methylene chloride decreased from $7x10^{-6}$ to $5.3x10^{-6}$ when polymorphism was included in the calculation.

Jonsson and Johanson (2001) calculated the excess cancer risk from methylene chloride by using Bayesian statistics. They refined and extended their previously developed population PBPK model for methylene chloride by simultaneously fitting extensive human toxicokinetic data from 27 male volunteers by using Markov chain Monte Carlo simulation. They then calculated excess cancer risk for lifetime exposures to methylene chloride, using Monte Carlo simulation and data on GSTT1 gene frequencies in the Swedish population. Their results confirmed and extended the previous study by El-Masri et al (1999). Their estimated mean and median excess cancer risks of exposure to 1 ppm of methylene chloride were $7.8x10^{-7}$ and $6.1x10^{-7}$, respectively.

David et al. (2006) assessed the cancer risk of methylene chloride exposure by using PBPK modeling and probabilistic methodology. Using previously developed PBPK models, the authors developed a cancer risk assessment by applying the model to humans and incorporating all available human exposure data sets in a Bayesian analysis. Metabolic data for individual subjects from five human studies were combined into a data set, and population values were derived by use of Markov chain Monte Carlo analysis. The mean unit risk estimated for exposure to 1 $\mu g/m^3$ of methylene chloride over a lifetime from this model was $1.05x10^{-9}$, considering both liver and lung tumors. This value is lower than the US EPA unit risk estimate ($4.7x10^{-7}$) by a factor of 400. Given the addition of the distribution of genetic polymorphisms in the GST pathway, the unit risks ranged from 0 (since a segment of the population consists of non-conjugators) up to $2.70x10^{-9}$ (at the 95^{th} percentile), with a median value of $9.33x10^{-10}$.

2.2.2 Oral Exposure

2.2.2.1 Death

Chang et al. (1999) reported a case of a 49-year-old male who intentionally ingested 300 mL of methylene chloride. At eight hours post-ingestion, his carboxyhemoglobin (COHb) level was 35%. He was hypertensive, tachycardic, and anuric, and he developed metabolic acidosis. The patient also exhibited symptoms of abnormal liver functions, renal failure, tachypnea, dyspnea, pneumonia, respiratory failure, pulmonary edema, confusion, and agitation. He became comatose and eventually died in the hospital on day nine.

2.2.2.2 Systemic Effects

Chang et al. (1999) reported six cases of patients who ingested methylene chloride. Five of the cases recovered after hospitalization. The most common symptoms seen in these patients were central nervous system depression, tachypnea, and corrosive gastrointestinal injury. In addition, renal failure, hepatic failure, and acute pancreatitis occurred in the two most severe cases. Methylene chloride ingestion often results in increased COHb levels that can be used as an indicator of exposure. However, COHb levels were measured in only two of these six patients. The peak COHb levels for the two patients were 8.4% and 35%, with outcomes of recovery and death, respectively.

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

El-Masri et al. (1999) investigated the effect of incorporating information on GSTT1 genetic polymorphism into a model of the risk distribution of methylene chloride in a human population. Their method used Monte Carlo simulation and PBPK modeling, combined with available information of ethnic distributions and polymorphism variability within each ethnic group of the population. The PBPK model used was based on earlier models, and it estimated the amount of DPX caused by metabolism of methylene chloride (as the surrogate for cancer risk estimates). Their results showed that the average and median risk estimates were approximately 30% lower when protective GSTT1 polymorphisms were included in the calculations.

In an effort to better understand the variability of methylene chloride inhalation toxicokinetics in humans, Jonsson et al. (2001) developed a population model for methylene chloride with an emphasis on the mixed-function oxidase (MFO) metabolic pathway. They merged *in vitro* metabolism data and partitioned with inhalation toxicokinetic data from five human volunteers, using Markov chain Monte Carlo simulations within a population PBPK model. The authors used the basic PBPK model by Andersen et al. (1987) that was subsequently modified by Reitz et al. (1988) and added a compartment for working muscle. Their results indicate that the metabolic capacity for the MFO pathway in humans is slightly larger than previously estimated and that the inter-individual variability of the MFO pathway is smaller than indicated by *in vitro* samples.

Jonsson and Johanson (2001) calculated the excess cancer risk from methylene chloride by using Bayesian statistics. They refined and extended their previously developed population PBPK model for methylene chloride (Jonsson et al. 2001) by simultaneously fitting extensive human toxicokinetic data from 27 male volunteers using Markov chain Monte Carlo simulation. They then calculated excess cancer risk for lifetime exposures to methylene chloride by using Monte Carlo simulation and data on GSTT1 gene frequencies in the Swedish population. Their results confirmed and extended the previous study by El-Masri et al. (1999). The estimated mean and median excess risks of exposure to 1 ppm of methylene chloride were calculated as $7.8x10^{-7}$ and $6.1x10^{-7}$, respectively.

Sweeny et al. (2004) re-analyzed the results of kinetic studies performed by DiVincenzo and Kaplan (1981) to obtain individual kinetic constants for human volunteers exposed to methylene chloride. Sweeney and co-workers then modified the Anderson et al. (1987, 1991) PBPK model, using this human kinetic data for methylene chloride, and assessed inter-individual variability in the rate of oxidative metabolism. The model fit to the data was improved by adding a component for extrahepatic metabolism of methylene chloride to the model structure and by optimizing the rate of oxidative metabolism in the liver for each individual. The modified PBPK model suggested a relatively narrow range in human hepatic activity toward methylene chloride.

Marino et al. (2006) applied Bayesian PBPK and dose-response modeling to mice in support of an improved cancer risk assessment of methylene chloride. In their analysis, Marino et al. (2006) used the basic model structure developed by Anderson et al. (1987), which describes the metabolism of methylene chloride in the liver and lung by both an oxidative pathway (cytochrome P450) and a GST pathway. Several experimental data sets were used to calibrate the mouse model. The results show that internal dose metrics from their calibrated mouse model are 3- to 4-fold higher than values used by the EPA to derive the EPA's unit risk factor for methylene chloride.

In order to derive acute exposure guideline levels (AEGLs) focusing on short-term non-cancer risks, Bos et al. (2006) combined the Anderson et al. (1991) and Reitz et al. (1997) PBPK models and extended the resulting model to include an estimation of maximum COHb formation,

in addition to central nervous system (CNS) depression. The combined PBPK model also accounted for the saturable step in the biotransformation of methylene chloride and considered the genetic polymorphism of the GSTT1. The model simulated accurately both COHb formation and methylene chloride concentration in the brain, as verified by data from two experimental studies. Using this combined and extended model, the authors derived acute exposure guideline levels for methylene chloride. The values from this model that have been accepted as interim AEGLs are presented in Chapter 7, Table 7-1.

David et al. (2006) built upon the basic PBPK model structure developed by Andersen et al. (1987, 1991) and refined by Marino et al. (2006) for the mouse by applying the model to humans. The David et al. model included a secondary extrahepatic/extrapulmonary component to account for higher methylene chloride metabolism at low concentrations, as recommended by Sweeney et al. (2004). Unlike previously published assessments, this model used GSH flux (a GST-metabolite) as the dose metric. In addition, it incorporated GST polymorphisms and included individual values for metabolism of methylene chloride from all available human data sets (four studies) to estimate the population parameters by using probabilistic statistics. By use of the calibrated human model, the mean unit risk estimated for exposure to 1 μg/m^3 of methylene chloride over a lifetime was $1.05x10^{-9}$, considering both liver and lung tumors. This value is lower than the US EPA's unit risk estimate ($4.7x10^{-7}$) by a factor of 400. With the addition of the distribution of genetic polymorphisms in the GST pathway, the unit risks ranged from 0 (since a segment of the population are non-conjugators) up to $2.70x10^{-9}$ (at the 95^{th} percentile), with a median value of $9.33x10^{-10}$.

2.5 RELEVANCE TO PUBLIC HEALTH

Systemic Effects

Genotoxic Effects. Hu et al. (2006) transfected V79 cell lines with the mouse glutathione transferase theta 1 gene (mGSTT1) and compared the resulting cell line to the parent cell line

(MZ) to determine how the construct affects methylene chloride metabolism and resulting DNA damage and cytotoxicity. Cytotoxicity assays did not reveal a difference in the two cell lines when they were exposed to methylene chloride. After methylene chloride treatment, a significant dose-dependent increase in tail movement in the V79 MZ cells was observed, as opposed to the significant dose-dependent decrease observed in V79 mGSTT1 cells. The study results indicated that V79 mGSTT1 cells are able to metabolize methylene chloride to a genotoxic and cytotoxic metabolite, most likely formaldehyde**.**

Wantanabe et al. (2007) conducted a study to measure dihaloalkane-induced GSH linked DNA adducts in Fischer 344 rats (male) and B6C3F1 mice (male and female). Methylene chloride was administered by intraperitoneal injection (5 mg/kg body weight), and livers and kidneys were collected to isolate DNA. None of the four known GSH-DNA adducts were detected following methylene chloride exposure.

2.9 INTERACTIONS WITH OTHER CHEMICALS

A semi-permeable membrane device (SPMD) was used to assess the relative effectiveness of two extractants, methylene chloride and triolein (a neutral lipid), for the removal and analysis of PCBs and PAHs from various stages of sewage treatment in Beijing, China. Results showed that the triolein-SPMD combination was more effective than methylene chloride extraction for all PAHs analyzed, for almost all of the PCB congeners (except PCBs 110 and 120 at the last stage of treatment), and for most of the substituted benzenes analyzed (other than xylenes and phenol at the intermediate stages) (Wang et al. 2001).

3. CHEMICAL AND PHYSICAL INFORMATION

No updated data.

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

No updated data.

5. POTENTIAL FOR HUMAN EXPOSURE

5.3.2 Transformation and Degradation

Attempting to develop an effective technology to purify methylene chloride-contaminated gas streams, Yu et al. (2006) identified *Psudomonas* sp. and *Mycobacterium* sp. as bacteria capable of utilizing methylene chloride as sole carbon and energy sources. The mixed culture of the two bacteria had high removal efficiencies (72–99%) in the bio-trickling filter and in flasks. Sodium chloride concentrations should be maintained lower than 35.1 g/L to optimize removal efficiency.

Methylobacterium strains have the ability to use methylene chloride for growth as the sole source of carbon and energy. Kayser et al. (2002) investigated which metabolic features are important for growth of methylotrophic bacteria with methylene chloride. They investigated whether the sole expression of the enzyme methylene chloride dehalogenase in highly related Methylobacterium strains would allow them to grow with methylene chloride. The study indicated that factors other than the dehalogenase are required for growth of Methylobacterium strains with methylene chloride.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Methylene chloride was generally not detected in the blood of 1,165 participants in the National Health and Nutrition Examination Survey (NHANES) 2003-2004 subsample of the United States population (CDC 2009).

Roelofs et al. (2003) investigated four Massachusetts companies, all able to reduce or eliminate methylene chloride use in operations. The authors suggested that a source reduction approach be considered for reducing or eliminating the possible hazards of methylene chloride exposure.

Estill et al. (2002) described a case study of a furniture stripping shop to demonstrate how methylene chloride exposures can be reduced to below the Occupational Safety and Health Administration permissible exposure limit by use of engineering and administrative controls. Beneficial controls included providing local exhaust ventilation at the stripping tank and rinsing area, providing adequate make-up air, adding paraffin wax to the stripping solution (as a barrier to evaporation), raising the level of the stripping solution in the tank, and discussing good work practices with employees.

Nieuwenhuizen et al. (2000) investigated four chlorinated hydrocarbons, including methylene chloride (at 5–200 ppm), that produce phosgene as a combustion product during shielded metal arc welding. Results indicated that the short-term maximum allowable concentration for phosgene was not reached at the maximum allowable concentration of methylene chloride.

6. ANALYTICAL METHODS

6.2 ENVIRONMENTAL SAMPLES

Analyzing air samples collected during the spraying application of paints, primers, resins, and glues in 15 companies, Preller et al. (2004) used a photo-ionization detector and charcoal tubes to investigate which exposure metrics best characterize peak inhalation exposure to organic solvents. The factors identified to most strongly characterize peak exposure were exposure intensity, frequency of peaks, and duration of peaks. Walton (2005) noted that the Preller study used both an incorrect voltage lamp and correction factor for methylene chloride (should have

used 11.32eV, instead of 10.6 eV). However, the main findings of the study (how to describe peak exposure profiles) were not affected, since the correlation between peak measures remains the same (Preller 2005).

To estimate methylene chloride concentrations in cultures and environmental samples during biodegradation experiments, Krausova et al. (2003) presented a spectrophotometric method. Concentration of methylene chloride was estimated from its rate of degradation through use of a coupled enzymatic assay of two reactions: one catalyzed by methylene chloride dehalogenase in the presence of glutathione and a second reaction catalyzed by formaldehyde dehydrogenase with nicotinamide adenine dinucleotide (NAD+).

7. REGULATIONS AND ADVISORIES

Table 7-1. Updated Regulations and Guidelines Applicable to Methylene chloride

Agency	Description	Information	Reference
NATIONAL			
Regulations and Guidelines:			
a. Air			
NIOSH	IDLH	2,300 ppm [a]	NIOSH 2007
NAC/AEGL	AEGL-1[b] (interim)		EPA 2010
	10 minutes	290 ppm	
	30 minutes	230 ppm	
	60 minutes	200 ppm	
	AEGL -2[b] (interim)		
	10 minutes	1700 ppm	
	30 minutes	1200 ppm	
	60 minutes	560 ppm	
	4 hr	100 ppm	
	8 hr	60 ppm	
	AEGL-3[b] (interim)		
	10 minutes	12,000 ppm	
	30 minutes	8,500 ppm	
	60 minutes	6,900 ppm	
	4 hr	4,900 ppm	
	8 hr	2,100 ppm	
STATE			
b. Water			
New Jersey	Ground water quality criteria	3 μg/L	NJ Dept Env Protec 2009

[a]NIOSH potential occupational carcinogen
[b]AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

AEGL = Acute Emergency Exposure Guideline Levels; IDLH = immediately dangerous to life or health; NAC/AEGL = National Advisory Committee for AEGLs ; NIOSH = National Institute for Occupational Safety and Health; Interim AEGLs are established following review and consideration by the NAC/AEGL of public comments on proposed AEGLs. Interim AEGLs are available for use by organizations while awaiting NRC/NAS peer review and publication of final AEGLs.

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