Addendum to the Toxicological Profile for Chloromethane

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CONTENTS

1. EXECUTIVE SUMMARY 3

2. HEALTH EFFECTS 4
2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE 4
2.2.1 Inhalation Exposure 4
2.2.1.8 Cancer 4
2.3 TOXICOKINETICS 4
2.5. RELEVANCE TO PUBLIC HEALTH 5
2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE 5

3. CHEMICAL AND PHYSICAL INFORMATION 6

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL 6

5. POTENTIAL FOR HUMAN EXPOSURE 6
5.2 RELEASES TO THE ENVIRONMENT 6
5.3 ENVIRONMENTAL FATE 6
5.3.2 Transformation and Degradation 6
5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES 6

6. ANALYTICAL METHODS 7

7. REGULATIONS AND ADVISORIES 7

8. REFERENCES 7

ADDENDUM FOR CHLOROMETHANE
Supplement to the 1998 Toxicological Profile for Chloromethane

Background Statement

This addendum for chloromethane supplements the Toxicological Profile for Chloromethane that was released on December 1998.

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 Priority List 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" [§ 9604 (i)(1)(B)].

The purpose of this addendum is to provide, to the public, other federal, state, and local agencies a non-peer reviewed supplement of the scientific data that was published in the open peer-reviewed literature since the release of the profile in 1998.

Chapter numbers in this addendum coincide with the toxicological profile for Chloromethane (1998). This document should be used in conjunction with the profile. It does not replace it.

1. EXECUTIVE SUMMARY

Very little new information was found for chloromethane that is relevant to the Toxicological Profile. No association between occupational exposure to chloromethane and pancreatic cancer was found, but chloromethane produced chromosome aberrations in cultured mammalian cells. Humans that lack the enzyme glutathione-*S*-transferase T1 (GSTT1) virtually metabolize no chloromethane. Cigarette smoke emits 4 magnitudes of chloromethane concentrations than is typically found in the urban environment, and exposed cigarettes smokers and those passively exposed to the smoke are potentially exposed to greater amounts of chloromethane than the otherwise general population. New strains of bacteria that can degrade chloromethane in natural soil and water systems have been identified. Additional data confirm that major releases of chloromethane are from tropical plants and wood-rotting fungi, along with the chemical reactions that occur in the oceans or from chemicals reactions that occur from combustion of grass, wood, charcoal, and coal. As noted in Section 5.2 of the Toxicological Profile for Chloromethane published in December 1998, up to 99% of the chloromethane released to the environment comes from natural sources.

2. HEALTH EFFECTS

Very little new information regarding health effects of chloromethane was located in the literature since the publication of the Toxicological Profile for Chloromethane in December 1998.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

2.2.1 Inhalation Exposure

2.2.1.8 Cancer

An extensive population-based case-control study to determine which industries may be related to an increased risk of pancreatic cancer was conducted (Kernan et al. 1999). Death certificates of 63,097 persons who had died from pancreatic cancers in 24 U.S. states from 1984–1993 were obtained and the occupations were determined. In addition, potential exposure to specific solvents, including chloromethane was assessed. No association with exposure to chloromethane was found.

2.3 TOXICOKINETICS

As discussed in Section 2.3.3 of the Toxicological Profile for Chloromethane, conjugation of chloromethane via glutathione transferase is the main form of metabolism in humans and animals. The human population consists of fast metabolizers, medium metabolizers and non-metabolizers due to a genetic polymorphism of the enzyme glutathione-*S*-transferase T1 (GSTT1). Because of this unique polymorphism, these populations have been further studied in the development of physiologically-based pharmacokinetic (PBPK) models to assess the reliability of such models in general (Johanson et al. 1999; Jonsson et al. 2001) and to investigate how the genetic polymorphism affects the metabolism and disposition of chloromethane specifically in vivo (Lof et al. 2000).

Lof et al (2000) exposed 24 volunteers, eight with high, eight with medium, and eight with no GSTT1 activity to10 ppm chloromethane for 2 hours. The concentration of chloromethane was measured in inhaled air, exhaled air and blood. The experimental data was used in a 2-compartment model with pathways for exhalation and metabolism. Respiratory uptake averages were 243, 148 and 44 μmol in high, medium and no GSTT1 activity groups, respectively. During the first 15 minutes of exposure, the concentration of chloromethane in blood rose rapidly and then plateaued. The blood concentrations of chloromethane were similar in all three groups during the 2-hour exposure. At the end of exposure, the blood concentrations declined rapidly in the high and medium metabolizing groups, but declined more slowly in the group lacking GSTT1 activity. The half-times were 1.7, 2.8 and 3.8 minutes, respectively for the first phase and 44, 48, and 60 minutes, respectively, for

the second phase Metabolic clearance was 4.6 and 2.4 L/min in the high and medium GSTT1 groups, but nearly absent in the non-metabolizing group. The rate of exhalation clearance was similar among the three groups, but the non-metabolism group had much higher concentrations of chloromethane in exhaled air after exposure.

Jonsson et al. (2001) used the data from the GSTT1 deficient group from the Lof et al. (2000) study to develop a standard PBPK model for chloromethane with six tissue compartments: lung, working muscle, resting muscle, well-perfused tissues, liver, and fat. The model also included uptake of chloromethane via ventilation, and all elimination was accounted for by exhalation because these individuals lacked the ability to metabolize chloromethane. The model was fit to the experimental data. Although the model provided a good general model, the concentrations in exhaled air and blood were slightly overpredicted. The authors noted that the use of non-metabolizing subjects allowed them to assess the kinetics of a volatile chemical without interference from metabolism and to obtain greater knowledge on physiological parameters, but using chloromethane as a model compound had limitations, such as, low solubility of chloromethane in blood, low blood:air partition coefficient, and rapid decay during first minutes after exposure.

Species differences in the GSTT1 activity for chloromethane in liver and kidney tissues from mice, rats, hamsters and all three phenotypes of humans were studied in vitro (Thier et al. 1998). No GSTT1 activity was found in either tissue of the non-metabolizing phenotypic human subjects. The GSTT1 activity in the liver and kidney tissue from the high GSTT1 humans were twice as high as in the low metabolizing group, and two to seven times higher in the liver tissues than in the kidney tissues of either group. The GSTT1 activities in decreasing order were mice > high GSTT1 humans > rat > low GSTT1 humans > hamster > GSTT1-deficient humans.

2.5. RELEVANCE TO PUBLIC HEALTH

Genotoxic Effects

Chloromethane was positive for chromosome aberrations in cultured Chinese hamster ovary cells with and without the presence of S9 mix (Asakura et al. 2008).

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

The 1998 Toxicological Profile for Chloromethane discusses the difference between fast eliminators and slow eliminators of chloromethane but states that the extent to which chloromethane reacts with glutathione in humans is not known. The more recent studies discussed above (Jonsson et al. 2001; Lof et al. 2000; Their et al. 1998) provide information on the GSTT1 activity among the polymorphic phenotypes in humans. As noted by Lof et al. (2001), persons with low ability or those unable to

conjugate chloromethane via GSTT1 may be more susceptible to the neurological effects of chloromethane.

3. CHEMICAL AND PHYSICAL INFORMATION

No updated information.

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

No updated information.

5. POTENTIAL FOR HUMAN EXPOSURE

5.2 RELEASES TO THE ENVIRONMENT

Several studies confirm information in the Toxicological Profile for Chloromethane that a major sources of release of chloromethane to the air comes from tropical plants (Yokouchi et al. 2002; Yokouchi et al. 2000; Yokouchi et al. 2007) and wood-rotting fungi (Saxena et al. 1998) and to soil from wood-rotting fungi (Moore et al. 2005). As noted in the Profile, up to 99% of chloromethane released to the environment is from natural sources, such as from chemical reactions that occur in the oceans or from chemicals reactions that occur from combustion of grass, wood, charcoal, and coal.

An anthropogenic source of chloromethane may be cigarette smoke, about 5% in the United States, as estimated by (Novak et al. 2008). Novak et al. (2008) collected smoke samples from burning cigarettes in special smoking adaptors into 2 L canisters and analyzed the smoke for chloromethane using gas chromatography. The chloromethane concentrations were about 30–500 ppmv (1.5–5.3 mg/cigarette) compared with about 500 pptv (parts per trillion) in typical urban air.

5.3 ENVIRONMENTAL FATE

5.3.2 Transformation and Degradation

Six new *Hyphomicorbium* strains, strain CMC related to *Aminobacter* spp, two previously isolated bacteria CC495 and IMB-1, and a Gram-positive isolate related to *Nocardiodides* spp. from a variety of pristine terrestrial, freshwater, estuarine and marine environments were as chloromethane utilizing bacteria (McAnulla et al. 2001).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

People who smoke cigarettes and those exposed passively to the smoke have a higher exposure to chloromethane as noted by Novak et al. (2008).

6. ANALYTICAL METHODS

No updated information.

7. REGULATIONS AND ADVISORIES

No updated information.

8. REFERENCES

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