ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR 1,1-DICHLOROETHENE

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
Atlanta, GA 30333

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CONTENTS

ADDENDUM for 1,1-Dichloroethene
Supplement to the 1994 Toxicological Profile for 1,1-Dichloroethene

Background Statement

This addendum the Toxicological Profile for 1,1-Dichloroethene supplements the profile that was released in 1994.

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 1994.

Chapter numbers in this addendum coincide with the Toxicological Profile for 1,1-Dichloroethene (1994). 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

2.2.1.2 Systemic Effects

Inhalation exposure (4 hours) of 1,1-dichloroethene (180–200 ppm) to fasted rats produced both liver injury and renal toxicity. Pretreatment of rats with amino-oxyacetic acid significantly reduced the nephrotoxic and hepatotoxic effects of 1,1-dichloroethene (Cavelier et al., 1996).

2.2.1.3 Immunological and Lymphoreticular Effects

Ban et al. (2003) showed that inhalation exposure to 1,1-dichloroethene increased the interferon-gamma release in the lung-associated lymph nodes, as well as the numbers of IgM producing B cells against sheep red blood cells, indicating that this chemical may promote sensitization through an adjuvant effect—by increasing antigen-presenting activity.

In a follow-up study, Ban et al. (2006) tested the adjuvant effect of 10 ppm 1,1-dichloroethene in female mice sensitized to ovalbumin (OVA) without using alum. During the OVA-sensitization period, these mice were exposed by inhalation to 1,1-dichloroethene for 6 hours/day for four consecutive days. After two OVA-intratracheal challenges, a mild Th2 immune response was observed in the OVA-exposed groups, a response that was characterized by a mild increase in serum specific IgE level, in local Th2 cytokine production, and in lung inflammatory reaction. Exposure to 1,1-dichloroethene alone markedly increased the Th2 cytokine levels above the levels observed in the groups exposed to OVA alone. A synergistic effect of 1,1-dichloroethene and OVA on cytokine production did not occur; however, 1,1-dichloroethene did potentiate the production of IgE, an influx of inflammatory cells, and goblet cell hyperplasia in the 1,1-dichloroethene plus OVA-sensitized mice (Ban et al., 2006).

2.2.2 Oral Exposure

2.2.2.2 Systemic Effects.

Hepatic Effects. NTP (1982) conducted 14-day studies in male and female rats and mice administered 1,1- dichloroethene by gavage in corn oil at 0, 10, 50, 100, 500, or 1,000 mg/kg. Hemorrhagic necrosis of the liver was observed in all rats that died at 500 and 1,000 mg/kg and in all mice at 1000 mg/kg. In the same study, rats and mice were administered 1,1-dichloroethene by gavage in corn oil at 0, 5, 15, 40, 100, or 250 mg/kg five times per week for 13 weeks. Three female rats receiving 250 mg/kg body weight per day died during the first week of the study. At 250 mg/kg body weight per day, the three female rats that died showed severe centrilobular necrosis. Minimal to moderate hepatocytomegaly was seen in the rest of the rats at 250 mg/kg body weight per day. Minimal to mild hepatocytomegaly was seen in 6/10 male rats and 3/10 female rats that received 100 mg/kg body weight per day. No biologically significant changes were observed in rats that received 40 mg/kg body weight per day or below. In mice, centrilobular necrosis of the liver was observed in 5/10 males and 5/10 females that received 250 mg/kg body weight per day and 2/10 males and 2/10 females that received 100 mg/kg body weight per day. No biologically significant changes in the liver occurred in mice receiving 40 mg/kg body weight per day or below.

The NTP also conducted 104-week chronic toxicity and carcinogenicity studies of 1,1-dichloroethene in male and female mice (2 or 10 mg/kg-day) and rats (1 or 5 mg/kg-day) by gavage in corn oil (NTP, 1982). The results of histopathological examination indicated an increased incidence of necrosis of the liver in high-dose male and low-dose female mice.

Liver tissue damage was observed in mice following single oral doses of 1,1-dichloroethene (100, 150, 200 mg/kg) as reflected by a decreased centrilobular G-6-Pase stain (Ban et al. 1998).

Renal Effects. Renal tissue damage was observed in mice following single oral doses of 1,1-dichloroethene (100, 150, 200 mg/kg) as reflected by an increase in damaged tubules (Ban et al., 1998).

1,1-Dichloroethene caused renal toxicity (damage to approximately 50% of proximal tubules) in mice following a single oral dose (200 mg/kg). Renal toxicity was inhibited by gavage pretreatment of mice with amino-oxyacetic acid, the β-lyase inactivator (Ban et al., 1995).

The NTP conducted 104-week chronic toxicity and carcinogenicity studies of 1,1-dichloroethene in male and female F344 rats by gavage in corn oil at 0, 1, or 5 mg/kg-day (NTP, 1982). The results of histopathological examination indicated chronic renal inflammation in male rats (26/50, 24/48, 43/48) and female rats (3/49, 6/49, 9/44). The increase was statistically significant only in males.

Other Systemic Effects. Mean body weight was significantly depressed at 500 mg/kg body weight per day and above in a 14-day study of rats (NTP 1982). In the same study, rats and mice were administered 1,1-dichloroethene by gavage in corn oil at 0, 5, 15, 40, 100, or 250 mg/kg five times per week for 13 weeks. The mean body weight was depressed 13% for male rats receiving 250 mg/kg body weight per day compared with controls. In mice, at 100 mg/kg body weight per day, there was a decrease in mean body weight in males (14%) but not in females. No biologically significant change in mean body weight was observed at lower exposures.

2.2.2.3 Immunological and Lymphoreticular Effects

Ban et al. (1998) reported the appearance of immunosuppressive activity in the serum of mice following single oral doses of 1,1-dichloroethene (100, 150, 200 mg/kg). All doses provoked liver and kidney damage. During the peak level of liver damage (200 mg/kg), a serum-borne immunosuppressive effect was also at its highest level. Examination of sera cytokine levels showed an increase of tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) at 6 hours after administration, followed by a decrease toward a baseline level. This study suggests that the immunosuppressive effect in sera of mice treated with 1,1-dichloroethene may result from tissue damage, and that the increased levels of TNF-alpha and IL-6 in sera may contribute to this effect (Ban et al., 1998).

2.2.2.6 Developmental Effects

Congenital cardiac defects in rat fetuses were observed in a study in which Sprague-Dawley rats were given water with high (110 ppm) or low (0.15 ppm) doses of 1,1-dichloroethene during prepregnancy only, during prepregnancy and pregnancy, or during pregnancy alone. 1,1-Dichloroethene delivered exclusively in the period before pregnancy caused no increase in congenital cardiac malformations over the control level. However, rats exposed both before and during pregnancy had a significantly greater number of fetuses with congenital cardiac malformations. Other fetal variables, including noncardiac congenital abnormalities, showed no significant difference between control and treated groups (Dawson et al., 1993). The results of this study are contradicted by a three-generation rat study (Nitschke et al., 1983) that reported no biologically significant effects on growth or survival after exposure to 1,1-dichloroethene via drinking water.

2.2.3 Dermal Exposure

The ability of 1,1-dichloroethene to cause skin sensitization was tested by using the local lymph node assay (Warbrick et al., 2001). Groups of mice were exposed topically on the dorsum of both ears to 25 µl of various concentrations daily for 3 consecutive days. 1,1-Dichloroethene failed to induce a positive response at any concentration tested.

2.3 RELEVANCE TO PUBLIC HEALTH

Substantial information exists regarding the effects of 1,1-dichloroethene in animals after inhalation and oral exposure; this information is summarized in section 2.4 of the Toxicological Profile for 1,1-Dichloroethene. The liver, kidney, and possibly the lungs can be considered target organs for 1,1-dichloroethene by both routes of exposure. Additional recent animal studies discussed in this addendum are summarized below.

Systemic Effects

Hepatic and Renal Effects. Acute, intermediate, and chronic oral exposure and acute inhalation exposure to 1,1-dichloroethene in mice and rats cause renal and liver toxicity (Ban et al., 1995,

1998; Cavelier et al., 1996; NTP 1982). Renal and liver toxicity can be inhibited by pretreatment of mice and rats with amino-oxyacetic acid, a β-lyase inactivator (Ban et al., 1995; Cavelier et al., 1996).

Immunological Effects. Immunosuppressive activity, which coincided with peak kidney and liver damage, was reported in the serum of rats following an oral dose of 1,1-dichloroethene (Ban et al., 1998). Inhalation studies (Ban et al., 2003, 2006) indicated that 1,1-dichloroethene may promote sensitization through an adjuvant effect.

Developmental Effects. Rats exposed to 1,1-dichloroethene both before and during pregnancy had a significantly greater number of fetuses with congenital cardiac malformations. Other fetal variables, including noncardiac congenital abnormalities, showed no significant difference between control and treated groups (Dawson et al., 1993). However, the results of this study are contradicted by a three-generation rat study (Nitschke et al., 1983) that reported no biologically significant effects on growth or survival.

Genotoxic Effects. 1,1-Dichloroethene was shown to induce mitotic chromosome malsegregation in the diploid strain P1 of *Aspergillus nidulans* (Crebelli et al., 1995).

2.6 TOXICOKINETICS

2.6.3 Metabolism

Dowsley et al. (1999) investigated the cytochrome P450-mediated metabolism of 1,1-dichloroethene by human lung and liver cells. The major metabolites detected were the 1,1-dichloroethene epoxide-derived glutathione conjugates 2-(S-glutathionyl)acetyl glutathione and 2-S-glutathionyl acetate. The acetal of 2,2-dichloroacetaldehyde was detected at low levels. This study also determined that CYP2E1 catalyzes the formation of the epoxide in the liver and, in some individuals, in the lung (Dowsley et al., 1999).

A study that investigated change patterns of the cytochrome P450 and glutathione s-transferases in rats orally exposed to 1-1 dichloroethene found that total cytochrome P450 was significantly

decreased, CYP2C11 was greatly decreased, and CYP1A1/2 was slightly reduced. In addition, liver cytosolic GST activity was enhanced, but serum GST activity was not affected (Wang et al., 1999).

Jones et al. (2003), investigated products of 1,1-dichloroethene biotransformation *in vivo* in rats treated by oral gavage with 50 mg/kg. The investigation revealed the presence of three glutathione conjugates, *S*-carboxymethyl glutathione, *S*-(cysteinylacetyl)glutathione, and a product of the intramolecular rearrangement of the metabolite, *S*-(2-chloroacetyl)glutathione, which had not been previously described in-vivo. In addition, several *S*-carboxymethylated proteins were identified in the bile, and total biliary protein concentration was decreased.

The metabolites of 1,1-dichloroethene identified from mouse hepatic and lung microsomal incubations were dichloroethene-epoxide (major metabolite), 2,2-dichloroacetaldehyde, and 2-chloroacetyl chloride (Dowsley et al., 1995, 1996). These metabolites undergo secondary reactions, including oxidation, conjugation with GSH, and hydrolysis. The major products formed were the GSH conjugates 2-(S-glutathionyl)acetyl glutathione and 2-S-glutathionyl acetate (Dowsley et al., 1995, 1996). Low levels of the acetal of 2,2-dichloroacetaldehyde were also formed, with relatively higher levels of this acetal observed in the lung versus the liver microsomes. Preincubation of microsomes with CYP2E1-inhibitory monoclonal antibody resulted in 50% inhibition of formation of metabolites derived from the dichloroethene-epoxide (Dowsley 1996).

Simmonds et al. (2004) demonstrated that both CYP2E1 and CYP2F2 catalyze the bioactivation of 1,1-dichloroethene to the epoxide in lung tissue of mice, and the authors demonstrated that CYP2E1 is the high-affinity enzyme involved in 1,1-dichloroethene bioactivation (Simmonds et al., 2004).

Woodard and Moslen (1998) characterized the effects of 1,1-dichloroethene (50 mg/kg via gavage) on the biliary secretion of proteins and phospholipids in rats. 1,1-Dichloroethene treatment caused a rapid decrease in total biliary protein output to approximately 50% of basal levels, a decrease that persisted for the entire experimental period (4 hours). There was a rapid

transient increase in lysosomal enzymes, but then came a progressive decrease to approximately 10% basal levels. Canalicular membrane enzymes increased by 15-fold, and secretion of phospholipids into bile decreased rapidly in treated rats. The authors postulate that 1,1-dichloroethene treatment results in functional impairment of proteins in the canalicular membrane (Woodard and Moslen 1998).

3. CHEMICAL AND PHYSICAL INFORMATION

No updated data

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

No updated data

5. POTENTIAL FOR HUMAN EXPOSURE

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.2 Water

A national assessment in 2006 by the U. S. Geological Survey reported the detection of 1,1-dichloroethene in 19 domestic well samples (of 1,207 well samples). In addition, 1,1-dichloroethene was detected at a concentration greater than the U.S. EPA's maximum contaminant level in one sample out of 2,400 sampled wells (Rowe et al., 2007). The wells were sampled during 1985–2002.

An earlier assessment by the U.S. Geological Survey of untreated, ambient groundwater wells between 1985 and 1995 identified 1,1-dichloroethene in 3% of wells in urban areas (n=406) and in 0.3% of wells in rural areas (n=2542). A few of these detections were above the maximum contaminant level (Squillace et al., 1999).

In an analysis of 70 private residential wells in South Carolina from August 2000 to February 2001, 1,1-dichloroethene was detected in two wells, with one well exceeding the maximum contaminant level (Aelion and Conte 2004).

In the area down-gradient of the Butz Landfill in Jackson Township, Pennsylvania (which was added to the National Priorities List [NPL] in 1989), 1,1-dichloroethene was detected in private residential well water at a maximum level of 14.6 μg/l . It was also detected in on-site and off-site monitoring wells (ATSDR 1996). An NPL site in Florida, called Florida Petroleum Reprocessors, also detected 1,1-dichloroethene in groundwater in on-site and off-site private wells (ATSDR 1999).

6. ANALYTICAL METHODS

No updated data

7. REGULATIONS AND ADVISORIES

Minimal Risk Levels (MRLs) from the 1994 Toxicological Profile are unchanged:
Intermediate-duration inhalation MRL = 0.02 ppm
Chronic-duration oral MRL = 0.009 mg/kg/day

The EPA revised its RfD and RfC after publication of the 1994 Toxicological Profile for 1,1-Dichloroethene. The current EPA oral RfD is 0.05 mg/kg/day, calculated from the $BMDL_{10}$ of 4.6 mg/kg/day for liver toxicity in a chronic bioassay in rats (Quast et al., 1983), using a total uncertainty factor of 30 and a modifying factor of 1. The EPA derived an RfC of 0.2 mg/m^3 calculated from the $BMCL_{HEC}$ for liver toxicity of 6.9 mg/m^3 in a chronic bioassay in rats (Quast et al., 1986), using a total UF of 30 and an MF of 1. The EPA has given 1,1-dichloroethene a Group C weight-of evidence carcinogenicity classification [possible human carcinogen] (IRIS 2009).

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