ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR ETHION

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ADDENDUM FOR ETHION
Supplement to the 2000 Toxicological Profile for Ethion

Background Statement

This addendum to the Toxicological Profile for Ethion 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 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 Ethion (2000). This document should be used in conjunction with the profile. It does not replace it.

1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS ETHION?

Ethion is a chemical pesticide used in agriculture, mainly to control insects on citrus trees. However, ethion is no longer sold in the United Sates. As of December 31, 2004, all uses of ethion in the United States were prohibited.

2. HEALTH EFFECTS

2.2.2 Oral Exposure

2.2.2.1 Death

Dewan et al. (2008) present a case report of an accidental fatal poisoning event in rural India. At a social ceremony, nine adult males and six children consumed a meal contaminated with ethion (dose levels unknown). Ten individuals (4 adults and all 6 children) died within 24 hours of exposure. One adult suffered cardiac arrest, with associated brain ischemia, and died 8 months later.

2.2.2.2 Systemic Effects

Respiratory Effects. Within 2-3 hours after consuming a meal contaminated with ethion, 15 individuals complained of difficulty in respiration (Dewan et al. 2008). Three of the individuals developed respiratory distress and died within a few hours of admission to the health center. One case of pulmonary edema was reported. Five patients survived and were transferred to another hospital, where 3 eventually recovered after atropine and pralidoxime treatment. The fourth patient was intubated and put on assisted ventilation for 20 days and eventually recovered. The fifth patient suffered cardiac arrest, with associated brain ischemia, was resuscitated and put on ventilator support, but remained unconscious and died 8 months later.

Gastrointestinal Effects. Gastrointestinal effects reported after consuming a meal contaminated with ethion included diarrhea, vomiting and abdominal pain (Dewan et al. 2008). These symptoms started within 2-3 hours after eating the meal.

Hematological Effects. Bhatti et al. (2011) studied the effect of vitamin E on ethion-induced biochemical and morphological alterations in erythrocytes. Rats were orally exposed to ethion at a daily dose of 2.7 mg/kg body weight for 7, 14, 21 and 28 days. Ethion exposure resulted in oxidative damage to erythrocyte membranes. Lipid peroxidation increased significantly with increasing duration (increased 79%, 145%, 241%, and 359% after 7, 14, 21, and 28 exposure days, respectively). Total lipid and phospholipid content was significantly decreased in the erythrocyte membranes, along with decreased membrane cholesterol levels. Compared with control animals, total lipids decreased 11% after 7 days and 35% after 28 days; phospholipids decreased 12% after 7 days and 50% after 28 days; cholesterol content decreased 21% at 14 days and 47% at 28 days. Activities of membrane-bound enzymes (Na+K+ ATPase and Mg2+ATPase) were also inhibited. Morphological alterations of the erythrocytes were observed. The group of rats that were coadministrated ethion (2.7 mg/kg) and vitamin E (50 mg/kg) showed significantly less damage to the erythrocytes (compared with the ethion-treated group), suggesting that vitamin E provided a protective effect.

Hepatic Effects. Oral ethion exposure to rats induced oxidative stress in the liver accompanied by histological alterations that diminished with vitamin E supplementation (Bhatti et al. 2010). Male albino Wistar rats were divided into four groups of six animals and treated for 7, 14, 21, and 28 days. Group 1 was the control group and received corn oil; group 2 received ethion at 2.7 mg/kg bodyweight/day; group 3 received vitamin E at 50 mg/kg body weight/day; and group 4 received ethion (2.7 mg/kg/day) and vitamin E (50 mg/kg/day). Ethion caused significant induction of oxidative damage in liver tissue with increased lipid peroxidation and decreased glutathione content. Lipid peroxidation increased 32%, 56%, 123% and 147% at 7, 14, 21, and 28 days, respectively. Glutathione content decreased 28%, 33%, 40%, and 47% at 7, 14, 21, and 28 days, respectively. A significant increase occurred in the activities of four antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase, and glutathione-S-transferase) beginning at day 7 and increasing through day 28. A significant decrease occurred in glutathione reductase activity. Histopathological examinations showed severe mononuclear infiltration in all portal areas, severe hydropic degeneration, and focal lobular hepatitis in the ethion treated group. Coadministration of vitamin E provided some protection against these ethion-induced histopathological and biochemical alterations in the liver.

Body Weight Effects. A significant decrease occurred in the body weight of male rats orally administered 2.7 mg/kg/day of ethion for 7–28 days (Bhatti et al. 2010). The longer the duration, the more pronounced the weight loss. This study also coadministered ethion (2.7 mg/kg/day) and vitamin E

(50 mg/kg/day) to a group of rats. This resulted in only a slight decrease in body weight when compared with control animals, suggesting a protective effect of vitamin E.

2.2.2.4 Neurological Effects

In the Dewan et al. (2008) report of food-related ethion poisoning of 15 people in rural India, three of the five survivors presented conscious, although they exhibited what the report authors described as clinical signs of organophosphate poisoning (specific symptoms not reported). On day 1, red blood cell cholinesterase levels for these three subjects were inhibited by approximately 17%, 58 % and 65%. The plasma cholinesterase level for one subject was within the normal range, but the other two subjects had almost 90% inhibition of plasma cholinesterase. These three subjects recovered after 1 week of atropine and pralidoximine treatment. They were discharged from the hospital after 25–27 days. The remaining two subjects required assisted ventilation. They had zero detectable red blood cell cholinesterase levels through day 8 post-exposure, and plasma cholinesterase levels were inhibited by 90%. One subject eventually recovered, but the other subject suffered cardiac arrest with brain ischemia and died eight months later.

Rats orally exposed to ethion at a daily dose of 2.7 mg/kg body weight for 7, 14, 21 and 28 days showed a significant decrease in erythrocyte acetylcholinesterase (Bhatti et al. 2011, 2010). Compared with control animals, a significant decrease of 27% occurred after 7 days, 33% after 14 days, 37% after 21 days and 42% after 28 days of treatment. Coadministration of ethion with vitamin E (50 mg/kg/day) also resulted in acetylcholinesterase decrease, but to a lesser degree than ethion treatment alone. This suggests that vitamin E mitigated ethion’s effect on acetylcholinesterase levels.

2.4 MECHANISMS OF ACTION

2.4.2 Mechanisms of Toxicity

The increase in lipid peroxidation in the livers of rats orally administered ethion at 2.7 mg/kg/day for 28 days suggests that ethion induces oxidative stress (Bhatti et al. 2010). Ethion has been shown to induce oxidative damage in erythrocyte membranes, with resultant alterations in erythrocyte membrane structure and function. Such alterations have been seen in both *in vivo* and *in vitro* studies, and include increased lipid peroxidation and decreases in phospholipid content and membrane bound enzymes (Bhatti et al. 2011; Singh 2006). However, an *in vitro* study of rat erythrocytes exposed to ethion by Singh et al.

(2004) showed a decrease of lipid peroxidation together with an increase in hemolysis and K^+ leakage. The authors postulated that the difference in lipid peroxidation between this *in vitro* study and *in vivo* studies might be due to ethion itself, rather than its metabolite, interacting with the erythrocyte membrane (Singh et al. 2004).

2.9 INTERACTION WITH OTHER CHEMICALS

Coadministration of vitamin E and ethion resulted in a decrease in ethion-induced toxicity in rats. Oral coadministration of ethion (2.7 mg/kg) and vitamin E (50 mg/kg) showed significant reductions of ethion-induced effects on erythrocytes, liver, body weight, and acetylcholinesterase levels, when compared with the ethion only treated group (Bhatti et al. 2010, 2011).

3. CHEMICAL AND PHYSICAL INFORMATION

No updated information.

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

Ethion is no longer sold in the United Sates. In 2001, the ethion registrants requested a voluntary cancellation of their products rather than commit to development of the additional data required by the U.S. Environmental Protection Agency (EPA) to assess risks for re-registration (EPA 2002). As of December 31, 2004, all uses of ethion in the United States were prohibited (EPA 2002). Ethion is also no longer used in Canada, where its registration was cancelled in 2003 (Health Canada 2001). However, other countries, including India and Australia, still produce or use ethion (Bhatti et al 2011; APVMA 2011).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Because ethion is no longer available in the United States, the potential for human exposure in this country is expected to occur via environmental exposures to ethion resulting from its past use as an insecticide.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.2 Water

Wilson and Foos (2006) examined 332 surface water samples for organophosphates. The samples were collected over a 365-day period from Ten Mile Creek in Ft. Pierce, Florida. Only ethion and diazinon were detected. Ethion was quantified in 19 samples, 18 of which were collected on consecutive days from August 1 to 18, 2001. The mean, maximum, minimum, and median ethion concentrations were 0.38, 0.61, 0.30, and 0.33 μg/L, respectively. The ethion-quantifiable samples were all collected following a heavy period of rainfall. This suggested ethion was transported via surface runoff from citrus groves in a sub-basin within the Indian River Lagoon watershed.

From April 1992 to December 2007, the South Florida Water Management District collected pesticide data for surface water and sediment samples (Pfeuffer 2011). The areas sampled included 34 sampling sites in 16 counties from Orlando to the Florida Keys. At all locations combined, ethion had 27 detections in surface water and 24 detections in sediment. Twenty-five of the surface water detections occurred in the citrus agriculture basin with an average concentration of 0.11 μg/L and a maximum concentration of 0.83 μg/L. The 20 sediment detections in this basin had an average and maximum concentration of 9.8 μg/kg and 46 μg/kg, respectively. Most of the surface water detections occurred during the growing season. After the 2001 voluntary cancellation of ethion, however, it has not been detected in surface water at this location since the August 2001 sampling event. The last sediment detection occurred during the October 2003 sampling event (Pfeuffer 2011).

5.6 EXPOSURES OF CHILDREN

Ethion has been detected in human breast milk/colostrum of mothers living in rural areas of Faizabad, India (Srivastava et al. 2011). Ethion was detected in six of 26 samples of colostrum, and in one of eight samples of breast milk.

6. ANALYTICAL METHODS

No updated information.

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Ethion

Agency	Description	Information	Reference
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	0.05 mg/m^3 [a,b]	ACGIH 2009
	TLV-basis (critical effect)	Cholinesterase inhibition	
c. Other			
ACGIH	Carcinogenicity classification	A4[c]	ACGIH 2009
DHHS	Carcinogenicity classification	No	NTP 2011

[a]Inhalable fraction and vapor notation: material exerts sufficient vapor pressure such that it may be present in both particle and vapor phases, with each contributing a significant portion of the dose at the TLV-TWA concentration.
[b]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, by contact with vapors, liquids, and solids.
[c]A4: not classifiable as a human carcinogen.

ACGIH = American Conference of Governmental Industrial Hygienists; DHHS = Department of Health and Human Services; NTP = National Toxicology Program; TLV = threshold limit value; TWA = time-weighted average

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