2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of ethion. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of

exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for ethion. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

Ethion is a pesticide, and its use is regulated under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Virtually all of the toxicity information on ethion is from unpublished studies performed

by the manufacturer and submitted for review to the EPA. A few of these studies were unable to be retrieved by ATSDR. In these cases, NOAEL and LOAEL values were taken from study summaries in "Guidance for the Reregistration of Pesticide Products Containing Ethion as the Active Ingredient" (EPA 1989d) and are so cited in the text.

2.2.1 Inhalation Exposure

2.2.1.1 Death

Male and female rats (number and strain not specified) were exposed to technical ethion via inhalation and the LC_{50} (lethal concentration, 50% kill), was calculated. The acute inhalation LC_{50} was 2.31 mg/m^3 for male rats and 0.45 mg/m^3 for females (Feiser 1983 as cited in EPA 1989d).

No studies were located regarding the following effects in humans or animals after inhalation exposure to ethion:

2.2.1.2 Systemic Effects

2.2.1.3 Immunological and Lymphoreticular Effects

2.2.1.4 Neurological Effects

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals afer inhalation exposure to ethion.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to ethion.

Several acute lethality studies have demonstrated the high toxicity of ethion by the oral route. In a study reporting results for 98 (single dose) pesticides, (Gaines 1969) LD_{50} (lethal dose, 50% kill) values for ethion via gavage were 65 mg/kg for male and 27 mg/kg for female Sherman rats. The minimum survival time was 3 hours for males and 4 hours for females. The maximum time to death was 9 days for males and 6 days for females. The lowest dose to kill a rat was 50 mg/kg for males and 20 mg/kg for females. LD_1 (lethal dose, 1% kill) values were calculated at 27 mg/kg/males and 15 mg/kg for females. In a toxicokinetic study in Sprague-Dawley rats (Selim 1985a), two of seven males died after a gavage dose of 100 mg/kg; clinical signs of toxicity preceding death included salivation, tremors, diarrhea, and convulsions. Five of seven females died after receiving 25 mg/kg. Female rats appear to be more susceptible to ethion than males, but no explanations have been proposed.

Multiple oral exposures to ethion at lower doses in animals have generally not resulted in fatalities. For example, no deaths occurred in pregnant Charles River rats receiving up to 2.5 mg/kg/day ethion by gavage over gestation days (Gd) 6–15 (Hoberman et al. 1983a) or pregnant New Zealand rabbits receiving up to 9.6 mg/kg/day over Gd 6–18 (Hoberman et al. 1983b).

In an intermediate-duration exposure to ethion in feed to groups of albino rats (25/dose/sex), survival was similar after 96 days at doses of #9 mg/kg/day in males and 10 mg/kg/day in females (Keller and Paynter 1958). No deaths occurred in the parental generation (F_0) in a three-generation reproductive study in CD rats (Enloe and Salamon 1985). Exposure to ethion in feed was #1.25 mg/kg/day for 236–238 days. One of a group of four female Beagle dogs was sacrificed in a moribund condition after 90 days of exposure to ethion in feed at a dose of 8.25 mg/kg/day (Bailey 1988). Clinical signs included emesis, dehydration, and thin body mass. The other females in the group and the males exposed at #6.9 mg/kg/day survived.

In a 2-year feeding study in Sprague-Dawley rats and CF_1 mice (Morrow 1985a, 1985b), survival was similar between control and treated groups. Exposures in rats were #2 mg/kg/day (80/dose/sex) and #1.2 mg/kg/day in mice (10–50/dose/sex).

All reliable LD_{50} values and LOAELs for death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.2 Systemic Effects

Most, if not all, of the systemic effects observed after oral exposure to ethion are the result of the neurological effects of this chemical (see Section 2.2.2.4).

The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. A 6-month-old boy who accidentally ingested 15.7 mg/kg ethion from a contaminated milk bottle presented with diaphragmatic respiration with shallow excursions and intercostal retraction (Comstock et al. 1967). Respiratory rate was 60/minute. Auscultation revealed generalized rales and rhonchi and inspiratory and expiratory wheezes. Symptoms appeared one hour following ingestion and were treated with atropine and Protopam® (pralidoxime). Approximately 5 hours after ingestion, respiratory arrest occurred and mechanical ventilation was necessary for the next 3 hours. Treatment with atropine and pralidoxime continued for 5 days until symptoms ceased. Follow-up examinations after 1 week, 1 month, and 1 year indicated that a complete recovery was made by this patient. The respiratory effects seen in this case are consistent with cholinergic overstimulation caused by ethion (see Section 2.2.2.4).

Histopathological examinations of respiratory tract tissues after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Cardiovascular Effects. Tachycardia was reported in a 6-month-old boy who accidentally ingested 15.7 mg/kg ethion (Comstock et al. 1967).

Blood pressure and pulse rate were measured in a group of 6 male volunteers (age range, 23–43 years) who were given ethion in corn oil solutions in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) via

Table 2-1. Levels of Significant Exposure to Ethion - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (Sherman)	once (GO)				50 M (lowest lethal dose; LD_{50} = 65 mg/kg)	Gaines 1969
						20 F (lowest lethal dose; LD_{50} = 27 mg/kg)	
2	Rat (Sprague-Dawley)	once (GO)				25 F (5 of 7 died)	Selim 1985a
						100 M (2 of 7 died)	
	Systemic						
3	Human	once (IN)	Resp			15.7 M (rales and rhonchi, wheezing, increased respirations)	Comstock et al. 1967
			Cardio			15.7 M (tachycardia)	
			Gastro		15.7 M (emesis, watery bowel movement, hyperactive bowels)		
			Renal		15.7 M (proteinuria, increased urinary WBC)		

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
4	Rabbit (New Zealand)	13 d Gd 6-18 1x/d (GO)	Renal	0.6 F	2.4 F (increased incidence of orange-colored urine)		Hoberman et al. 1983b
			Bd Wt		9.6 F		
	Neurological						
5	Human	once (IN)				15.7 M (muscular twitching, lack of coordination, flaccid paralysis and areflexia, excessive salivation, pinpoint pupils)	Comstock et al. 1967
6	Rat (Charles River)	10 d Gd 6-15 (GO)		0.6 F	2.5 F (hyperactivity in dams)		Hoberman et al. 1983a
7	Rat (Sprague-Dawley)	once (GO)		2		10 F (salivation, tremors, nose bleeding, urination, diarrhea and convulsions)	Selim 1985a
						100 M (salivation, tremors, nose bleeding, urination, diarrhea and convulsions)	
	Developmental						
8	Rat (Charles River)	10 d Gd 6-15 (GO)		0.6	2.5 (delayed ossification of the ischium and pubes)		Hoberman et al. 1983a

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
9	Rabbit (New Zealand)	13 d Gd 6-18 1x/d (GO)		2.4		9.6 (increased incidence of fused sterna centra)	Hoberman et al. 1983b
	INTERMEDIATE EXPOSURE						
	Systemic						
10	Human	21 + 21+ 21 + 3 d 3x/d (C)	Cardio	0.15 M			Palazzolo 1970
			Hemato	0.15 M			
			Musc/skel	0.15 M			
11	Rat (albino)	96 d ad lib (F)	Resp	10			Keller and Paynter 1958
			Cardio	10			
			Gastro	10			
			Hemato	10			
			Musc/skel	10			
			Hepatic	10			
			Renal	10			
			Endocr	10			
			Bd Wt	10			
12	Rat (albino)	30 d ad lib (F)	Bd Wt	10			Keller and Paynter 1958

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
13	Rat (Sprague-Dawley)	6 or 12 mo ad lib (F)	Resp	2			Morrow 1985a
			Cardio	2			
			Gastro	2			
			Hemato	2			
			Musc/skel	2			
			Hepatic	2			
			Renal	2			
			Endocr	2			
			Dermal	2			
			Ocular	2			
			Bd Wt	2			
14	Mouse (CF1)	6 mo ad lib (F)	Resp	1.2			Morrow 1985b
			Cardio	1.2			
			Gastro	1.2			
			Hemato	1.2			
			Musc/skel	1.2			
			Hepatic	1.2			
			Renal	1.2			
			Endocr	1.2			
			Bd Wt	1.2			
			Other	1.2			

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
15	Dog (Beagle)	90 d ad lib (F)	Resp	6.9 M 8.25 F			Bailey 1988
			Cardio	6.9 M 8.25 F			
			Gastro	6.9 M 8.25 F			
			Hemato	6.9 M 8.25 F			
			Musc/skel	6.9 M 8.25 F			
			Hepatic	6.9 M 8.25 F			
			Renal	6.9 M 8.25 F			
			Endocr	6.9 M 8.25 F			
			Dermal	6.9 M 8.25 F			
			Ocular	6.9 M 8.25 F			
			Bd Wt	6.9 M 8.25 F			
	Immunological/Lymphoreticular						
16	Rat (albino)	96 d ad lib (F)		10			Keller and Paynter 1958
17	Rat (Sprague-Dawley)	6 or 12 mo ad lib (F)		2			Morrow 1985a

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
18	Dog (Beagle)	90 d ad lib (F)		6.9 M 8.25 F			Bailey 1988
	Neurological						
19	Human	21 + 21+ 21 + 3 d 3x/d (C)		0.15 M			Palazzolo 1970
20	Rat (albino)	96 d ad lib (F)		1	3 F (42.4-48.6% erythrocyte AChE inhibition)	10 F (67.4-74.3% brain AChE inhibition; 100% erythrocyte AChE inhibition)	Keller and Paynter 1958
					3 M (45-55% erythrocyte AChE inhibition)	9 M (87-95% erythrocyte AChE inhibiton, 22-29% brain AChE inhibition)	
21	Rat (albino)	30 d ad lib (F)		0.3 F		3 F (70% brain AChE inhibition)	Keller and Paynter 1958
				3 M	9 M (34.1% brain AChE inhibition)		
22	Rat (Sprague-Dawley)	6 or 12 mo ad lib (F)		2			Morrow 1985a
23	Mouse (CF1)	6 mo ad lib (F)		1.2			Morrow 1985b

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
24	Dog (Beagle)	90 d ad lib (F)		0.06[b] M 0.71 F	0.71 M (23% brain AChE inhibition)	6.9 M (tremors, ataxia, emesis, miosis, 61-64% brain and 93-96% erythrocyte AChE inhibition) 8.25 F	Bailey 1988
	Reproductive						
25	Rat (albino)	96 d ad lib (F)		10			Keller and Paynter 1958
26	Rat (Sprague-Dawley)	6 or 12 mo ad lib (F)		2			Morrow 1985a
27	Mouse (CF1)	6 mo ad lib (F)		1.2			Morrow 1985b
28	Dog (Beagle)	90 d ad lib (F)		6.4 M 8.25 F			Bailey 1988

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	CHRONIC EXPOSURE						
	Systemic						
29	Rat (CD)	3 gen ad lib (F)	Resp	1.25			Enloe and Salamon 1985
			Cardio	1.25			
			Gastro	1.25			
			Musc/skel	1.25			
			Hepatic	1.25			
			Renal	1.25			
			Endocr	1.25			
			Dermal	1.25			
			Ocular	1.25			
			Bd Wt	1.25			
30	Rat (Sprague-Dawley)	18 or 24 mo ad lib (F)	Resp	2			Morrow 1985a
			Cardio	2			
			Gastro	2			
			Hemato	2			
			Musc/skel	2			
			Hepatic	2			
			Renal	2			
			Endocr	2			
			Dermal	2			
			Ocular	2			
			Bd Wt	2			

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
31	Mouse (CF1)	12, 18, or 24 mo ad lib (F)	Resp	1.2			Morrow 1985b
			Cardio	1.2			
			Gastro	1.2			
			Hemato	1.2			
			Musc/skel	1.2			
			Hepatic	1.2			
			Renal	1.2			
			Endocr	1.2			
			Bd Wt	1.2			
			Other	1.2			
Immunological/Lymphoreticular							
32	Rat (CD)	3 gen ad lib (F)		1.25			Enloe and Salamon 1985
33	Rat (Sprague-Dawley)	18 or 24 mo ad lib (F)		2			Morrow 1985a
Neurological							
34	Rat (CD)	3 gen ad lib (F)		1.25			Enloe and Salamon 1985
35	Rat (Sprague-Dawley)	18 or 24 mo ad lib (F)		2			Morrow 1985a

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
36	Mouse (CF1)	12, 18, or 24 mo ad lib (F)		1.2			Morrow 1985b
	Reproductive						
37	Rat (CD)	3 gen ad lib (F)		1.25			Enloe and Salamon 1985
38	Rat (Sprague-Dawley)	18 or 24 mo ad lib (F)		2			Morrow 1985a
39	Mouse (CF1)	12, 18, or 24 mo ad lib (F)		1.2			Morrow 1985b

Table 2-1. Levels of Significant Exposure to Ethion - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
40	Rat (CD)	3 gen ad lib (F)		1.25			Enloe and Salamon 1985

[a]The number corresponds to entries in Figure 2-1.

[b]Used to derive a minimal risk level of 0.002 mg/kg/day for acute and intermediate durations based on a no-observed-adverse-effect-level of 0.06 mg/kg/day for inhibition of erythrocyte acetylcholinesterase in dogs. Dose divided by an uncertainty factor of 10 for human variability and 3 for extrapolation of an animal study to humans. For the chronic duration, an additional modifying factor of 5 was applied to reflect uncertainties of possible non-cholinesterase actions over long periods of exposure, and to protect against possible susceptibility in children, resulting in a minimal risk level of 0.0004 mg/kg/day.

AChE = acetylcholinesterase; ad lib = ad libitum; Bd Wt = body weight; (c) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; (GO) = gavage in oil; gen = generation; Gd = gestation day; Hemato = hematological; IN = ingestion; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; WBC = white blood cells; wk = week(s); x = time(s); yr = year(s).

Figure 2-1. Levels of Significant Exposure to Ethion - Oral

Acute (≤14 days)

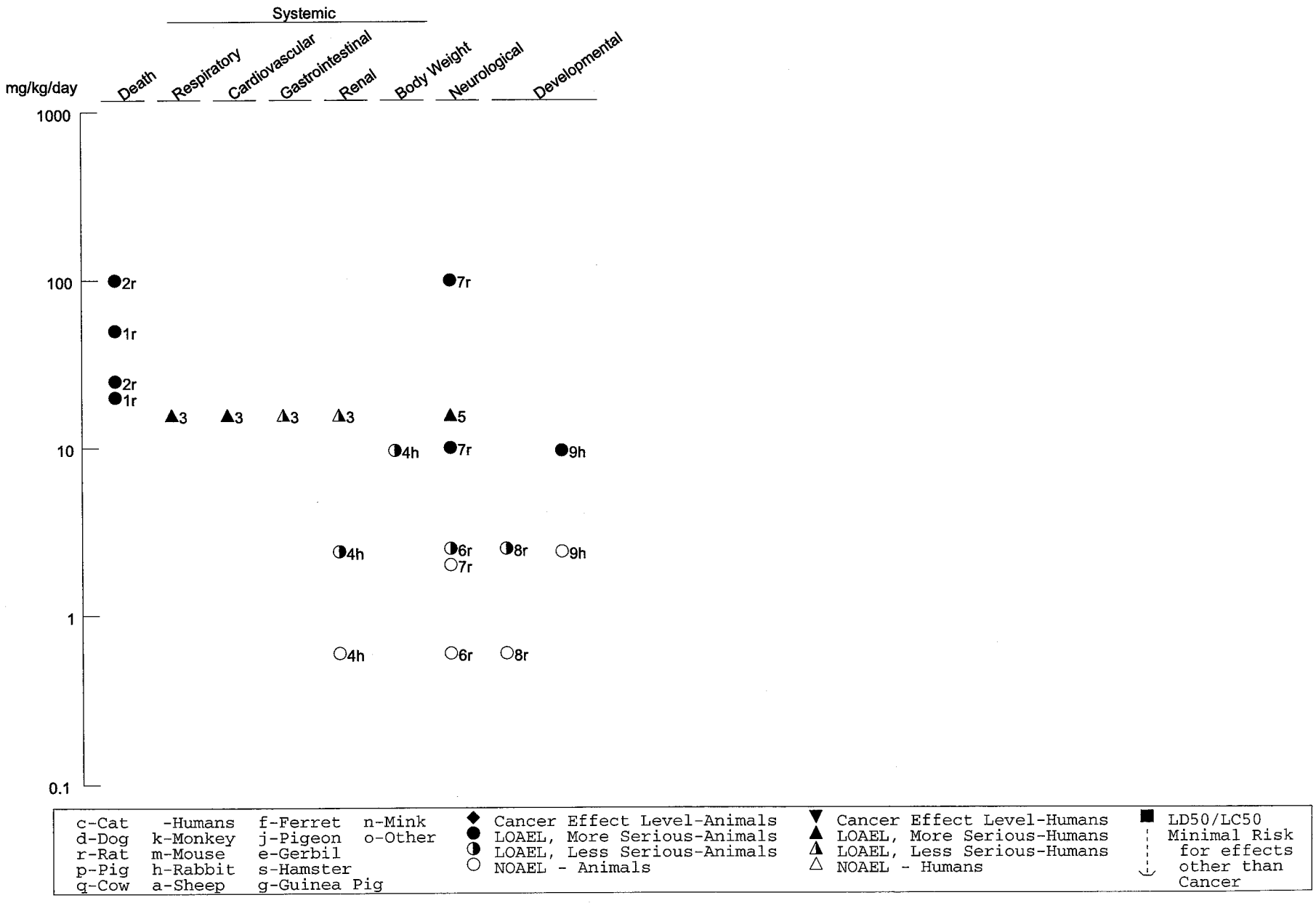


Figure 2-1. Levels of Significant Exposure to Ethion - Oral (Continued)

Intermediate (15-364 days)

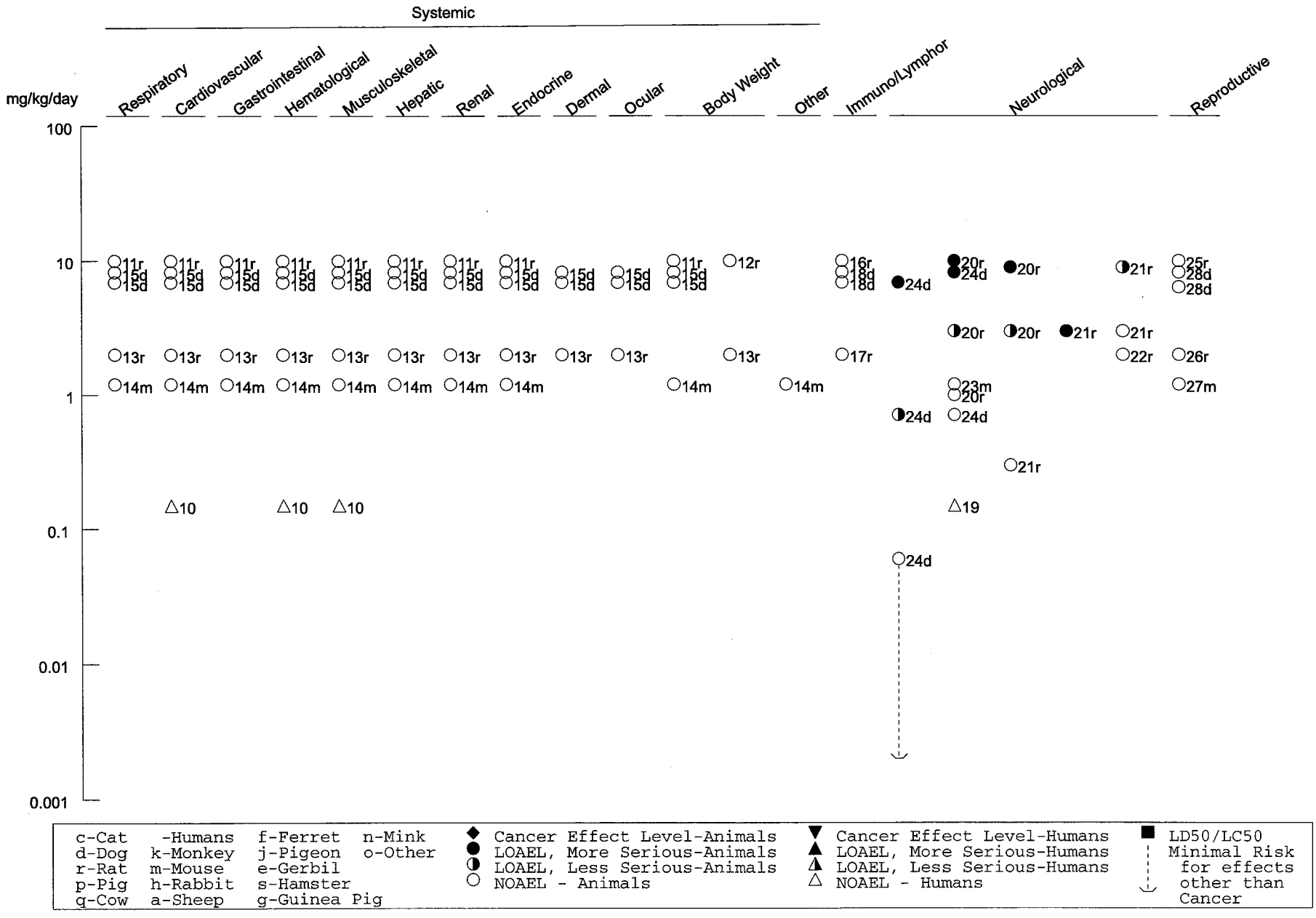
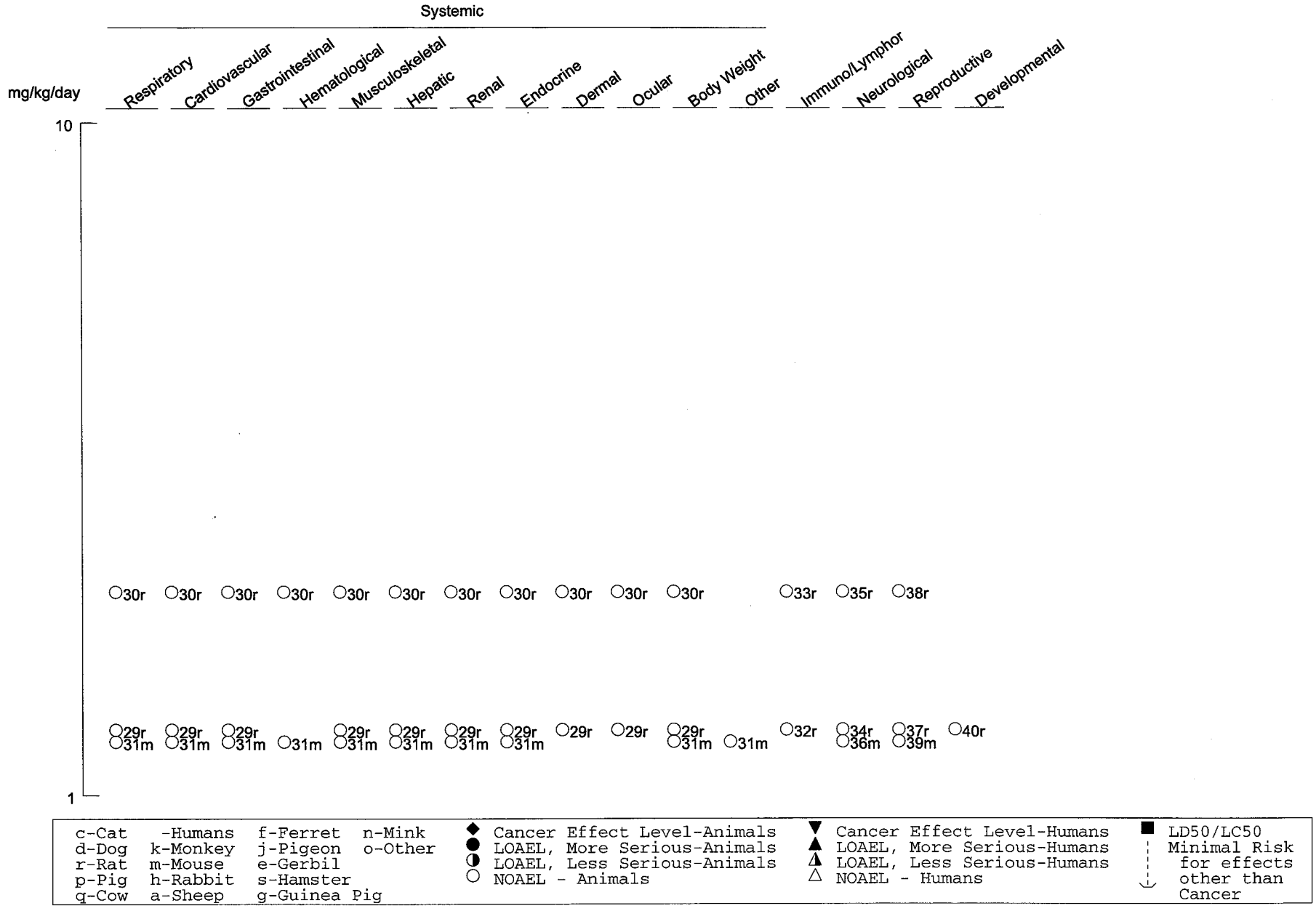


Figure 2-1. Levels of Significant Exposure to Ethion - Oral (Continued)

Chronic (≥365 days)



gelatin capsule (Palazzolo 1970). Doses were 0.05 mg/kg/day for 21 consecutive days, 0.075 mg/kg/day for the next 21 days, 0.10 mg/kg/day for the next 21 days, and 0.15 mg/kg/day for the next 3 days. Controls (n=4; age range, 22–40 years) received gelatin capsules containing corn oil. No differences were noted between the control and test groups or between individual pre-treatment, treatment, or post-treatment results for blood pressure or pulse rate.

Histopathological examinations of cardiovascular tissues (heart, aorta) after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Gastrointestinal Effects. Gastrointestinal effects reported in a 6-month-old boy who accidentally ingested 15.7 mg/kg ethion (Comstock et al. 1967) included frothy saliva 1 hour after ingestion and a watery bowel movement at 90 minutes. Bowel sounds were hyperactive and an episode of emesis occurred 5 hours after ingestion.

Diarrhea was reported in Sprague-Dawley rats exposed to ethion by gavage at 10 mg/kg in females and 100 mg/kg in males (Selim 1985a). Severe signs of neurotoxicity (convulsions) were also present. The gastrointestinal effects seen in both cases are consistent with cholinergic overstimulation of the gastrointestinal tract.

Histopathological examinations of gastrointestinal tract tissues after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Hematological Effects. Significant hematological effects have not been observed in two cases of human exposure to ethion. In a poisoning case of a 6-month-old boy who accidentally ingested 15.7 mg/kg ethion, hematocrit, hemoglobin level, and red blood cell (RBC) and platelet counts were

normal (Comstock et al. 1967). White blood cell (WBC) counts were initially slightly depressed but returned to normal after 1 day.

Similar results were seen for intermediate-duration oral exposure in a group of 6 male volunteers (age range, 23–43 years) who were given ethion in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) via gelatin capsule (Palazzolo 1970). Doses were 0.05 mg/kg/day for 21 consecutive days, 0.075 mg/kg/day for the next 21 days, 0.1 mg/kg/day for the next 21 days, and 0.15 mg/kg/day for the next 3 days. Controls (n=4; age range, 22–40 years) received gelatin capsules containing corn oil. Blood studies (hemoglobin concentration, hematocrit, RBC, and total and differential leukocyte counts) were performed on days -15 and -1 of the pretreatment period, at the end of each of the 4 treatment periods, and after a 19-day recovery period after dosing ended. No differences were noted between the control and test groups or between individual pre-treatment, treatment, or post-treatment results for any of the parameters.

Analysis of hematological parameters after oral exposure to ethion in animals has shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Musculoskeletal Effects. Oral exposure to ethion can result in muscle tremors and fasciculations. These effects are discussed in Section 2.2.2.4, Neurological Effects.

The effect of intermediate-duration oral exposure to ethion on muscle tone was assessed in a group of 6 male volunteers (age range, 23–43 years) who were given ethion in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) via gelatin capsule (Palazzolo 1970). Doses were 0.05 mg/kg/day for 21 consecutive days, 0.075 mg/kg/day for the next 21 days, 0.1 mg/kg/day for the next 21 days, and 0.15 mg/kg/day for the next 3 days. Controls (n=4; age range, 22–40 years) received gelatin capsules containing corn oil. Muscle tone was assessed at the beginning and end of each treatment period. No differences were noted between the control and test groups or between individual pre-treatment, treatment, or post-treatment results.

Histopathological examinations of musculoskeletal tissues (bone, skeletal muscle) after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to ethion.

Histopathological examinations of the liver after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Renal Effects. Proteinurea and increased urinary WBC counts were observed in a severely intoxicated 6-month-old boy who accidentally ingested 15.7 mg/kg ethion (Comstock et al. 1967).

An increased incidence of orange-colored urine was observed in pregnant New Zealand rabbits receiving ethion by gavage at 2.4, or 9.6 mg/kg/day during Gd 6–18 (Hoberman et al. 1983b). This effect was not observed at 0.6 mg/kg/day. Urinalysis was not performed.

Histopathological examinations of the kidney and bladder after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to ethion.

Histopathological examinations of endocrine tissues (pituitary, thyroid, parathyroid, thymus, adrenals) after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to ethion.

Histopathological examinations of the skin after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Ocular Effects. Histopathological examinations of the eye after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to ethion.

An unspecified body weight decrease occurred in New Zealand rabbit does receiving 2.4 mg/kg/day ethion via gavage over Gd 6–18. No effect on body weight was seen at 0.6 mg/kg/day (Hoberman et al. 1983b). No effect was observed on body weight in male and female dogs receiving #0.71 mg/kg/day in the diet for 13 weeks (Bailey 1988).

Body weight decreases accompanied by reduced food consumption have been observed in New Zealand rabbit does receiving 9.6 mg/kg/day ethion via gavage over Gd 6–18 (Hoberman et al. 1983b) and in male and female Beagle dogs receiving 6.9 and 8.25 mg/kg/day, respectively, in feed (Bailey 1988). In

other studies where doses were low enough that overt signs of cholinergic toxicity were not observed, body weight was unaffected (Keller and Paynter 1958; Morrow 1985a, 1985b).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological/lymphoreticular effects in humans after oral exposure to ethion.

Histopathological examinations of immunological/lymphoreticular tissues after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

2.2.2.4 Neurological Effects

Ethion exerts its toxic effects in humans and animals by inhibiting neural acetylcholinesterase. This enzyme, which is present at cholinergic synapses throughout the central and peripheral nervous systems, is responsible for hydrolyzing acetylcholine released from the pre-synaptic terminal. If this enzyme is inhibited, acetylcholine accumulates in the synapse, resulting in increased firing of the post-synaptic neuron or increased neuroeffector activity. The consequences of increased cholinergic activity in the parasympathetic autonomic nervous system (muscarinic receptors) can include increased salivation, lacrimation, perspiration, miosis, nausea, vomiting, diarrhea, excessive bronchial secretions, bradycardia, frequent micturition, and incontinence. The effects of increased neuroeffector activity on skeletal muscles (nicotinic receptors) can include muscle fasciculations, cramps, muscle weakness, and depolarization-type paralysis. Effects on cholinergic synapses in the central nervous system (predominantly muscarinic) can result in drowsiness, fatigue, mental confusion, headache, convulsions, and coma. These classical symptoms of organophosphate neurotoxicity increase in severity and rapidity of onset in a dose-dependent manner (Ecobichon 1991).

Acetylcholinesterase is also present in erythrocytes where it is referred to as erythrocyte acetylcholinesterase. Both forms of acetylcholinesterase are produced by the same gene (Taylor et al. 1993). In

in vitro assays, erythrocyte and neural acetylcholinesterase are inhibited to roughly the same extent by exposure to organophosphate compounds with insecticide activity (Hayes 1982). Measurement of erythrocyte acetylcholinesterase is used as a surrogate for the inhibition of neural acetylcholinesterase. A cholinesterase capable of hydrolyzing acetylcholine is also produced by the liver and circulates in the blood. This enzyme, called plasma cholinesterase, is also inhibited by ethion and other organophosphates and can be used as a marker for exposure. The endogenous substrate of this enzyme is unknown. Experiments in both humans and animals show that this enzyme is inhibited by ethion at lower levels of exposure than required to inhibit neural or erythrocyte acetylcholinesterase (Bailey 1988; Palazzolo 1970).

A case report of a 6-month-old boy who accidentally ingested 15.7 mg/kg ethion from a contaminated milk bottle illustrates the toxic neurological effects of ethion (Comstock et al. 1967). Symptoms appeared one hour following ingestion. The child awoke crying and choking on frothy saliva. He was unable to control his head and limbs and subsequently had a watery bowl movement, and became limp (depolarization-type paralysis). Occasional twitching movements of the hands and around the mouth were noted. Upon admission to the hospital, he was slightly cyanotic with a generalized flaccid paralysis and areflexia. Respiration was increased (60/min) as was heartbeat (200/min). Pupils were pinpoint and nonreactive to light, and eye movements were purposeless. Salivation was excessive but not copious. Respiration was diaphragmatic with shallow respiratory excursions and intercostal retraction. Generalized rales and rhonchi and inspiratory and expiratory wheezes were noted. The liver and spleen were palpable. Bowel sounds were hyperactive. There were no abnormal heart sounds. Treatment with atropine and pralidoxime was started immediately. Approximately 5 hours after ingestion, respiratory arrest occurred and mechanical ventilation was necessary for the next 3 hours. Laboratory and roentgenologic studies showed protein in the urine and increased WBC in the urine. Treatment with atropine and pralidoxime continued for 5 days until symptoms ceased. Follow-up examinations after 1 week, 1 month, and 1 year indicated that a complete recovery was made by this patient.

A study with male volunteers established oral levels of exposure to ethion that had no adverse effect in humans (Palazzolo 1970). Male volunteers (n=6; age range, 23–43 years) were given ethion in corn oil solutions in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) of 0.05, 0.075, 0.1, and 0.15 mg/kg/day via gelatin capsule. Controls (n=4; age range, 22–40 years) received gelatin capsules containing corn oil. Medical histories and baseline plasma cholinesterase and erythrocyte acetylcholinesterase activities were determined prior to the start of the study (days -15, -11, -8, -4, and -1). Blood samples were taken prior

to dose administration. Subjects received 0.05, 0.075, and 0.1 mg/kg/day for 3 weeks each. Cholinesterase determinations were conducted on days 1, 3, 7, 14, and 21 for these dose levels. Subjects received 0.15 mg/kg for 3 days and cholinesterase determinations were made on days 1 and 3. A 19-day recovery period followed, and cholinesterase determinations were made on days 7, 12, and 19. At the beginning and end of each treatment period, pupil size, light reflex, eye accommodation, muscle tone, knee jerk, tongue tremor, and finger tremor were measured.

No effect on erythrocyte acetylcholinesterase was observed at any time during the study. No effect on plasma cholinesterase were observed at the 0.05 mg/kg/day dose level. Statistically significant decreases from pretreatment values were observed for all plasma cholinesterase determinations during the 0.075, 0.1, and 0.15 mg/kg/day treatment periods. A 16% decrease in plasma cholinesterase activity was seen in the 0.075 mg/kg/day group. Decreases of 23 and 31% were seen at the 0.1 and 0.15 mg/kg/day levels. A partial recovery of plasma cholinesterase levels was seen after 7 days of recovery, and a complete recovery was seen after 12 days. No clinical signs of adverse neurological effects were observed.

Severe neurological effects have also been observed in rats after a single oral exposure to ethion. Male Sprague-Dawley rats receiving 100 mg/kg ethion in corn oil by gavage had cholinergic signs, including salivation, tremors, nose bleeding, urination, diarrhea, and convulsions (Selim 1985a). Female rats exhibited these same signs at a 10-fold lower dose (10 mg/kg). In another acute oral exposure to ethion, groups of pregnant Charles River rats (n=25) were administered ethion via gavage at doses of 0, 0.2, 0.6, and 2.5 mg/kg from Gd 6 to 15 (Hoberman et al. 1983a). An increased incidence of hyperactivity was observed in dams in the 2.5 mg/kg group. Incidence was 2/25 in control, 3/25 at 0.2 mg/kg/day, 1/26 at 0.6 mg/kg/day, and 11/25 at 2.5 mg/kg/day ($p<0.01$). No other statistically significant physical signs were observed.

No reports were located describing organophosphate-induced delayed neurotoxicity (OPIDN) in humans after oral exposure to ethion. This is a syndrome observed in humans and some animal models after recovery from the acute cholinergic effects of certain organophosphorus compounds, for example tri-o-cresyl phosphate (Ecobichon 1991). The characteristic signs are disturbances of gait and ataxia beginning 7–14 days after exposure, progressing to severe muscular weakness and paralysis. Histological analysis reveals a "dying-back" type degeneration of motor fibers. This condition can be produced in chickens and cats but not in other test species. In a test to determine the potential of ethion to cause delayed neurotoxicity, 4 groups of 10 chickens received a single gavage dose of 2,792 mg/kg

ethion in corn oil after protection from acute cholinergic effects with 10 mg/kg atropine given intramuscularly (Roberts et al. 1986). Preliminary experiments determined that this dose is equal to the LD_{50} for ethion in chickens with atropine prophylaxis. A positive control group received 500 mg/kg of the known delayed neurotoxic agent tri-o-cresyl phosphate in corn oil, the control group received vehicle only. As expected, acute cholinergic signs were observed (inability to stand or walk, unsteadiness, lethargy) in the treated groups including deaths in 14 of the 40 chickens dosed. However, after recovery from the acute effects, no clinical or histopathological signs of delayed neurotoxicity were observed in the ethion groups. These signs were observed in the tri-o-cresyl phosphate group.

In an intermediate-duration feeding study in albino rats (Keller and Paynter 1958) significant inhibition of cholinesterase activities was observed at and above ethion doses of 3 mg/kg/day. Plasma cholinesterase was most sensitive to inhibition, followed by erythrocyte and then brain acetylcholinesterase. For example, for males receiving 9 mg/kg/day in the diet for 93 days, brain acetylcholinesterase was inhibited 22%, erythrocyte acetylcholinesterase 87%, and plasma cholinesterase 100%. This study also examined recovery of blood cholinesterases by putting the rats on a normal diet for 14 days after the 93 day exposure to ethion. Plasma cholinesterase recovered completely over this period while erythrocyte acetylcholinesterase recovered 63%. The no-effect level in this study was 1 mg/kg/day. In longer-term experiments in animals, groups of Sprague-Dawley rats (n=80/sex/group) were fed diets resulting in ethion consumption of 0, 0.1, 0.2, and 2 mg/kg/day; no effect on erythrocyte acetylcholinesterase was observed at 6, 12, or 18 months (Morrow 1985a). Significant neurological effects were observed in dogs receiving higher doses of ethion (Bailey 1988). Groups of dogs (n=4/sex/group) received ethion in the diet for 90 days, the average consumed was 0, 0.01, 0.06, 0.71, and 6.9 mg/kg/day for males and 0, 0.012, 0.07, 0.71, and 8.25 mg/kg/day for females. Clinical signs included ataxia, emesis, miosis, and tremors in the highest-dose groups. Strong inhibition of both brain (61–64%) and erythrocyte acetylcholinesterase (93–94%) was observed in the highest-dose groups. A reduction of 23% in brain acetylcholinesterase was observed in males at 0.71 mg/kg/day and 64% at 6.9 mg/kg/day, no effect was seen at 0.06 and 0.01 mg/kg/day. Plasma cholinesterase activity was inhibited in all groups except the low-dose males and females and was dose-related. No compound-related histopathological changes were observed in nervous system tissues (brain [with medulla/pons, cerebellar cortex, and cerebral cortex], sciatic nerve, or spinal cord [cervical, thoracic, lumbar]). Based on the NOAEL of 0.06 mg/kg/day for inhibition of brain acetylcholinesterase observed in this study, an MRL of 0.002 mg/kg/day for oral exposure for the acute and intermediate durations was calculated, as

well as a chronic-duration MRL of 0.0004 mg/kg/day. More information on this MRL and how it was derived is located in footnote b of Table 2-1, in Section 2.5, and in Appendix A of this profile.

In chronic-duration experiments, a 3-generation reproduction study in albino rats that consumed ethion in feed at 0, 0.1, 0.2, and 1.25 mg/kg/day, showed that plasma cholinesterase was inhibited in F_1 and F_2 females in the high-dose group. No effect was observed on erythrocyte acetylcholinesterase in any group (Enloe and Salamon 1985). In 2-year carcinogenicity bioassay experiments, no effect on erythrocyte acetylcholinesterase was observed at daily exposures of #2 mg/kg/day in rats and #1.2 mg/kg/day in mice (Morrow 1985a, 1985b).

2.2.2.5 Reproductive Effects

No studies regarding reproductive effects in humans after oral exposure to ethion were located.

In a 3-generation reproduction study, ethion was administered to F_0, F_1, and F_2 male (n=15) and female (n=30) rats in the diet at concentrations of 0, 0.1, 0.2, and 1.25 mg/kg/day. No effect on reproduction was observed (Enloe and Salamon 1985). Indices measured were: mating index (number of copulations/number of estrus cycles utilized), fertility index (number of pregnancies/number of copulations), gestation (number of parturitions/number of pregnancies), female fertility (number of pregnancies/number of females mated), and male fertility (number of sires/number of males mated).

Histopathological examinations of reproductive tissues after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988)

2.2.2.6 Developmental Effects

No studies regarding developmental effects in humans after oral exposure to ethion were located.

Three studies examining the effects of ethion on development in animals are available. Groups of pregnant Charles River rats (n=25) were administered ethion in a corn oil vehicle via gavage at doses of

0, 0.2, 0.6, and 2.5 mg/kg from Gd 6 to 15 (Hoberman et al. 1983a). Dams were observed and skeletal examinations were performed on the fetuses. Fetuses from the 2.5 mg/kg group had an increased incidence of delayed ossification of pubes. Groups of pregnant New Zealand rabbits (n=17) received ethion via gavage at doses of 0, 0.6, 2.4, and 9.6 mg/kg from Gd 6 to 18 (Hoberman et al. 1983b). Does were observed for clinical signs. Does in the 2.4 and 9.6 mg/kg/day groups had an increased incidence of orange-colored urine; however, this was not considered to be a toxic effect. Additionally, does in these groups had decreased body weights (not specified). Food consumption was also reduced in the 9.6 mg/kg/day females. Fetuses in the 9.6 mg/kg/day group had an increased incidence of fused sterna centra.

In a 3-generation reproduction study, ethion was administered to F_0, F_1, and F_2 male (n=15) and female (n=30) rats in the diet at concentrations of 0, 0.1, 0.2, and 1.25 mg/kg/day. No effect was observed on pup viability, survival, body weight, or structural development (Enloe and Salamon 1985).

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to ethion. Twenty-four hours after a single oral dose (2 mg/kg), ethion induced a small, but statistically significant, increase in the frequency of sister chromatid exchanges in white Leghorn chicks (Bhunya and Jena 1994). No other studies on the genotoxicity of ethion following oral exposure in animals were located.

Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies regarding carcinogenicity in humans after oral exposure to ethion were located.

In 2-year carcinogenicity bioassays, groups of Sprague-Dawley rats (n=80/sex/group) receiving diets containing ethion at 0, 0.1, 0.2, and 2 mg/kg/day had similar tumor incidences (Morrow 1985a). Similar results were observed in CF_1 mice receiving 0, 0.113, 0.225, and 1.2 mg/kg/day (Morrow 1985b).

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans following dermal exposure to ethion.

In a study comparing LD_{50} values for 98 pesticides, including ethion, groups of 80 male and 60 female adult Sherman rats were dermally dosed with technical-grade ethion dissolved in xylene (Gaines 1969). The calculated LD_{50} value was 245 mg/kg for males and 62 mg/kg for females. The minimum survival time was 3 hours for males and 6 hours for females. The maximum time to death was 7 days for males and 3 days for females. The lowest dose to kill a rat was 150 mg/kg for males and 50 mg/kg for females. LD_1 values were calculated at 100 mg/kg for males and 34 mg/kg for females. The LD_{50} values for death in rats are shown in Table 2-2.

2.2.3.2 Systemic Effects

No studies were located regarding systemic effects in humans following dermal exposure to ethion. The only systemic effects reported in animals after dermal exposure to ethion are dermal effects in rabbits.

Dermal Effects. Groups of rabbits (n=6/sex/dose) received dermal applications of technical-grade ethion at doses of 0, 1, 3, 25, and 250 mg/kg for 21 days (Weiner 1985a as cited in EPA 1989d). An increased incidence of erythema and desquamation was observed at the application sites in both male and females of the 25 and 250 mg/kg group.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies regarding immunological and lymphoreticular effects in humans after dermal exposure to ethion were located.

Groups of guinea pigs (number and sex not specified) were dermally exposed to technical-grade ethion in a skin sensitization test (Freeman 1984 as cited in EPA 1989d). Ethion caused slight erythema which cleared within 48 hours. Ethion was determined not to be a skin sensitizer.

Table 2-2. Levels of Significant Exposure to Ethion - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
ACUTE EXPOSURE						
Death						
Rat (Sherman)	once				150 mg/kg M (lowest lethal dose; LD_{50} = 245 mg/kg) 50 mg/kg F (lowest lethal dose; LD_{50} = 62 mg/kg)	Gaines 1969

F = female; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level

2.2.3.4 Neurological Effects

No studies regarding neurological effects in humans after dermal exposure to ethion were located.

Inhibition of brain acetylcholinesterase was observed in rabbits after dermal exposure to ethion for 21 days at 1 mg/kg/day, (Weiner 1985a, 1985b as cited in EPA 1989d). The NOAEL in these studies was 0.8 mg/kg/day.

No studies were located regarding the following health effects after dermal exposure to ethion:

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

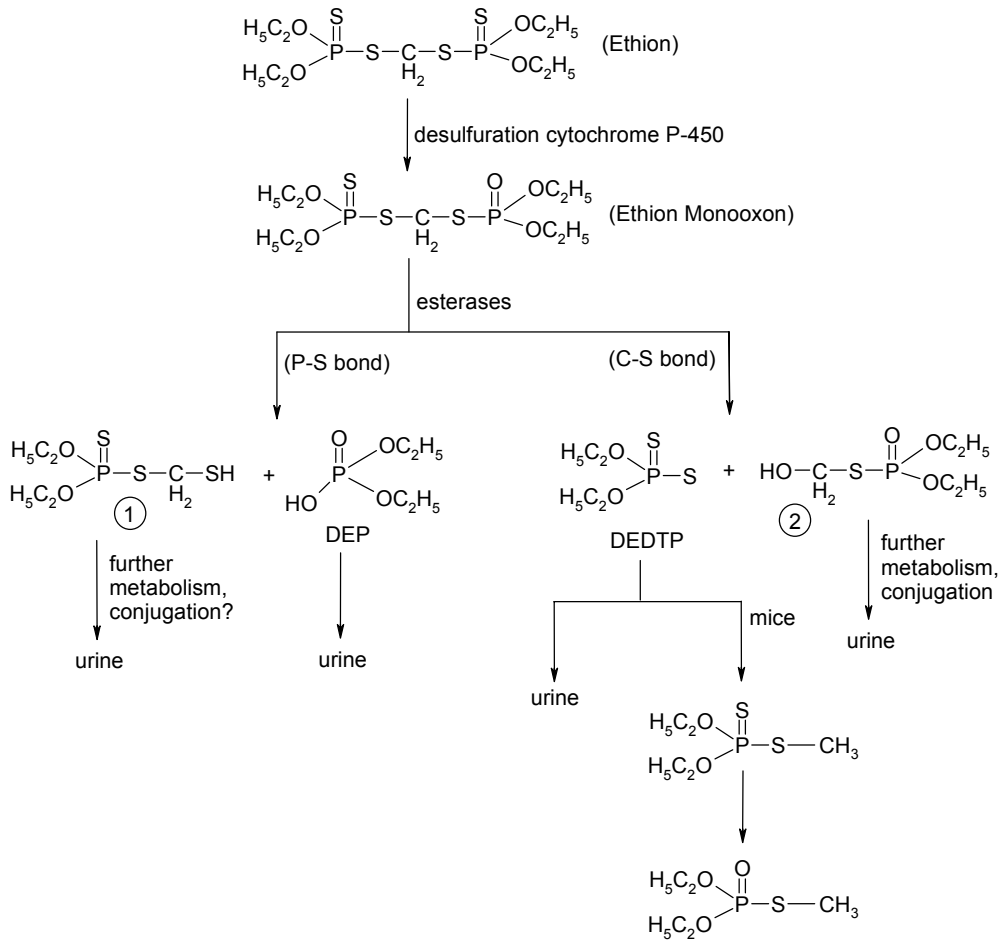
Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

2.3 TOXICOKINETICS

Ethion is a small (MW 384), lipid-soluble molecule that can be absorbed by passive diffusion through the lungs, gastrointestinal tract, or skin. Absorption appears to be rapid by the oral and dermal routes; the time course of absorption is inferred from the onset of clinical signs within 1 hour after accidental ingestion of ethion in a 6-month-old boy (Comstock et al. 1967) and deaths within 3–6 hours in dermally exposed Sherman rats (Gaines 1969). Ethion is desulfurated by cytochrome P-450 enzymes in the liver to its active form, ethion monoxon, which causes toxicity due to its potent inhibition of neural acetylcholin-esterase. Ethion and its oxon form can be detoxified by the action of esterases in the blood and liver, producing diethyl phosphate, diethyl thiophosphate, diethyl dithiophosphate, and other metabolites that have not been characterized. A proposed pathway for ethion metabolism is presented in Figure 2-2. Information on other aspects of toxicokinetics (distribution, metabolism, elimination/excretion) is limited by the nature of the studies available. Most toxicokinetic studies using ethion were designed to assess the persistence of ethion and its metabolites in meat or milk in the event that livestock were exposed to ethion-contaminated feed. Animals were exposed to [^{14}C-methylene]ethion and tissues harvested at

Figure 2-2. Proposed Mammalian Pathways of Ethion Biotransformation



Source: Mahajna et al. 1996; Nigg et al. 1993; Rao and McKinley 1969

DEP = diethylphosphate; DEDTP = diethyldithiophosphate
â O,O-diethyl-S-mercaptomethyldithiophosphate
ã O,O-diethyl-S-hydroxymethylphosphate

various times after exposure, and radioactivity was measured by liquid scintillation in ashed samples and expressed as ethion "equivalents." These experiments show that ethion and its metabolites are not stored in the body; however, since chemical characterization of the residues was not performed, no distinction can be made between the kinetics of the parent compound, active metabolite, and nontoxic metabolites.

2.3.1 Absorption

No information is available for any route as to whether absorption of ethion is different between children and adults or between juvenile and adult animals.

2.3.1.1 Inhalation Exposure

Absorption of ethion after inhalation exposure can be inferred from lethality reported in rats in an LC_{50} test (Feiser 1983 as cited in EPA 1989d). Time to death is not available from this summary, so no inference can be drawn as to how rapidly the ethion was absorbed.

2.3.1.2 Oral Exposure

Rapid absorption of ethion by the oral route in humans can be inferred from the onset of clinical signs within 1 hour after accidental ingestion of ethion in a 6-month-old boy (Comstock et al. 1967). Gastrointestinal absorption of ethion appears to be $80% in the rat based on residue studies performed with [^{14}C-methylene]ethion (Selim 1985a). In these studies, 75–85% of the total label was excreted in urine and 4–8% in feces. This pattern was the same whether labeled ethion was administered as a single dose or as the last dose after 14 days of dosing with unlabeled ethion.

2.3.1.3 Dermal Exposure

Dermal absorption of ethion has been measured in humans (Feldman and Maibach 1974). Radiolabeled ethion ([^{14}C]-specific activity not reported) was applied to the ventral forearm of 6 male volunteers at a concentration of 4 µg/cm^2 in acetone. The authors stated that this was equivalent to a thin film of a 0.25% solution. The skin sites were not protected, and the subjects were asked not to wash the area for 24 hours. All urine was collected for 5 days in a total of 8 samples (0–4, 4–8, 8–12, 12–24 hours, and the 4 subsequent 24-hour periods). Radioactivity in the urine was determined by combustion and liquid

scintillation counting. Results were calculated as percentage of applied dose corrected for incomplete urinary excretion using results from a parallel experiment where labeled ethion was administered intravenously. Over 24 hours, 3.3% of the dose was absorbed as calculated from urinary excretion of radioactivity.

In a study in goats dermally exposed with one application of 100 mg/kg ethion over a 600–700 cm^2 area, ethion in the blood was measured for 14 days (Mosha et al. 1990b). Unchanged ethion appeared in blood throughout the study and the $t_{1/2}$ for absorption was calculated as 85 hours, indicating that dermally applied ethion stays in the epidermis and is absorbed for a prolonged period.

2.3.2 Distribution

No information is available for any route as to whether distribution of ethion is different between children and adults or between juvenile and adult animals. Similarly, no information is available on whether ethion or its metabolites cross the placenta. However, given the high lipophilicity of ethion and ethion monoxon, it is probable that placental transfer occurs.

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution of ethion after inhalation exposure in humans or animals.

2.3.2.2 Oral Exposure

No studies were located regarding distribution of ethion after oral exposure in humans.

Seven days after rats received a single gavage dose of radiolabeled ethion, less than 1% of the radiolabel was detected in the body (blood, brain, heart, pancreas, leg muscle, lungs, adipose, spleen, bone, skin, hair, kidney, liver, gonads [uterus and ovaries for females, testes, seminal vesicle, and prostate for males]) (Selim 1985a). Total residues ranged from 0.21 to 0.34% of the original dose for females; and 0.18–0.28% for males. Similar results were obtained in a study where the radioactive dose was given after 14 consecutive daily doses of unlabeled ethion (Selim 1985a).

In a study designed to assess the presence of ethion in milk after oral exposure, two lactating goats (40 kg, strain not stated) were orally administered [^{14}C-methylene]ethion by capsule twice daily for 7 consecutive days (Jobsis and Zeitlow 1985). Test animals were sacrificed 4 hours after the final dose and the animals dissected. Tissues (blood, adductor muscle, pectoral muscle, liver, heart, kidney, peritoneal fat, and renal fat) along with daily milk samples taken during the test period were assayed for residues by combustion and liquid scintillation counting. Total daily dose was 1.12 mg/kg/day. The authors stated that this was comparable to a dietary level of 45–70 ppm in feed. Highest residue levels (radioactivity as ethion equivalents) were in liver (13–14 ppm) and kidney (7–9 ppm). Levels in muscle and heart tissues were approximately 1 ppm, and levels in fat were approximately 0.2 ppm. Levels in milk were approximately 1.2 ppm.

Unchanged ethion (the monoxon was not measured) was detected in goat milk after oral (~1.4% of administered activity) exposure to ethion. Equilibrium dialysis indicated that ethion was >99% bound to plasma proteins (Mosha et al. 1990b). Radioactivity derived from labeled ethion was present in goat milk after oral exposure (Jobsis and Zeitlow 1985); however, the chemical identity of the radioactivity was not determined.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of ethion after dermal exposure in humans. One animal study (Mosha et al. 1990b) examined the levels of ethion in goat milk following dermal exposure, reporting 0.04–0.05% of the total dose to be found in the milk. No other animal studies on the distribution of ethion following dermal exposure were located.

2.3.2.4 Other Routes of Exposure

A study by Mosha (1990b) examined the distribution of [^{14}C-methylene]ethion following a single intravenous administration in male and female goats. All tissues examined (kidney, liver, muscle, fat, heart, lung, and brain) had ^{14}C levels similar to or higher than the corresponding concentration in plasma, with the highest concentrations found in liver, kidney, and fat. No differences in distribution between male and female goats were noted.

2.3.3 Metabolism

While the basic features of ethion metabolism are known, detailed information is lacking. Like other organothiophosphate insecticides (chlorpyrifos, parathion), ethion is converted via desulfuration in the liver by cytochrome P-450 enzymes to its active oxygen analogue, ethion monoxon (Rao and McKinley 1969) (see Figure 2-2). It is not known if ethion monoxon can then be desulfurated to ethion dioxon. Ethion monoxon is a potent inhibitor of cholinesterases and exerts toxicity by reacting with and inhibiting neural acetylcholinesterase. The breakdown of ethion and ethion monoxon has not been characterized but is presumed to be by esterases in the blood and liver. Cleavage of the monoxon at the P-S bond would result in diethyl phosphate and a transient intermediate (O,O-diethyl-S-mercaptomethyldithiophosphate). Cleavage can occur in humans at both the P-S bond and the S-C bond, based on the detection of diethyl phosphate (P-S cleavage of the monoxon), diethyl thiophosphate (P-S cleavage of ethion or S-C cleavage of the monoxon), and diethyl dithiophosphate (S-C cleavage of ethion) in the urine of pest control workers using ethion (Nigg et al. 1993). Relative amounts were not reported. Evidence in mice for cleavage at the S-C bond and subsequent methylation of the sulfur has also been presented (Mahajna et al. 1996). Further metabolism of the product(s) of the esterase reaction continues but how it happens is unknown. Elimination from the body is mainly through excretion of water-soluble metabolites in the urine. Conjugation may occur, this is inferred from experiments where [^{14}C-methylene]ethion was administered orally to rats and the radioactivity in urine analyzed (Selim 1985b). Samples were extracted with ethyl acetate; the aqueous and organic phases were analyzed by high-performance liquid chromatography (HPLC). More than 99% of the urine radioactivity was in the aqueous phase. Another sample was acidified (presumably to hydrolyze conjugates) and also extracted with ethyl acetate. Acidification converted about 30% of the radioactivity in the aqueous phase to an organosoluble form, which may indicate that some of the products of ethion metabolism are present in urine as conjugates. Four to six radiolabeled metabolites were detected by HPLC, none migrated with standards for ethion, ethion monoxon, or ethion dioxon. None of the metabolites were specifically identified.

No information is available for any route as to whether the metabolism of ethion is different between children and adults or between juvenile and adult animals.

2.3.4 Elimination and Excretion

No information is available for any route as to whether elimination and excretion of ethion is different between children and adults or between juvenile and adult animals.

2.3.4.1 Inhalation Exposure

No studies were located regarding elimination or excretion following inhalation exposure to ethion in humans or animals.

2.3.4.2 Oral Exposure

No studies were located regarding elimination or excretion following oral exposure to ethion in humans.

Ethion and its metabolites were readily excreted from male and female Sprague-Dawley rats exposed to single and multiple dosing regimens of [^{14}C-methylene]ethion (Selim 1985a). A majority of the administered dose (75–85%) was excreted in urine. Most of the elimination occurred within 24 hours of dosing. Elimination also occurred by feces (4–8%) and respiratory gases (CO_2) (3–4%). Following oral exposure to 10 mg/kg [^{14}C]ethion in goats, 64% was excreted in the urine, 14% in the feces, and 1.7% in the milk (total recovery was 80%) (Mosha et al. 1990b).

2.3.4.3 Dermal Exposure

Excretion in urine accounted for 3.3% (SD +1.1%) of the [^{14}C]ethion radioactivity applied to the skin of volunteers for 24 hours over the 5 days following application (Feldman and Maibach 1974). Diethyl phosphate, diethyl thiophosphate, and diethyl dithiophosphate were detected in the urine of pest control workers using ethion and the carbamate pesticide, benomyl (Nigg et al. 1993). Total ethion metabolites (benomyl does not contain phosphorus) ranged from 0.30 to 7.0 ppm/day in a group of six workers; metabolites were not detected in two control workers not directly engaged in spraying. Relative amounts of the metabolites were not reported. Exposure is presumed to be primarily dermal. Unchanged ethion (the monoxon was not measured) was detected in goat milk after dermal exposure to ethion (Mosha et al. 1990b). A total of 0.04–0.05% of the dose appeared in the milk.

2.3.4.4 Other Routes of Exposure

Mosha (1990b) reported that following a single intravenous exposure to 2 mg/kg of [^{14}C-methylene]ethion in goats, one third of the administered activity was excreted in the urine within the first 24 hours. Two weeks following administration, a total of 66% of the administered activity was excreted in the urine, with another 8% found in the feces, and 4% in the milk (total recovery for the study was 78%). The identities of the excreted compounds were not determined. After intravenous exposure of 2 mg/kg [^{14}C] ethion to goats in another study, the peak of ethion in milk was 1.2 ppm (Mosha 1991).

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

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen

1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-3 shows a conceptualized representation of a PBPK model.

If PBPK models for ethion exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

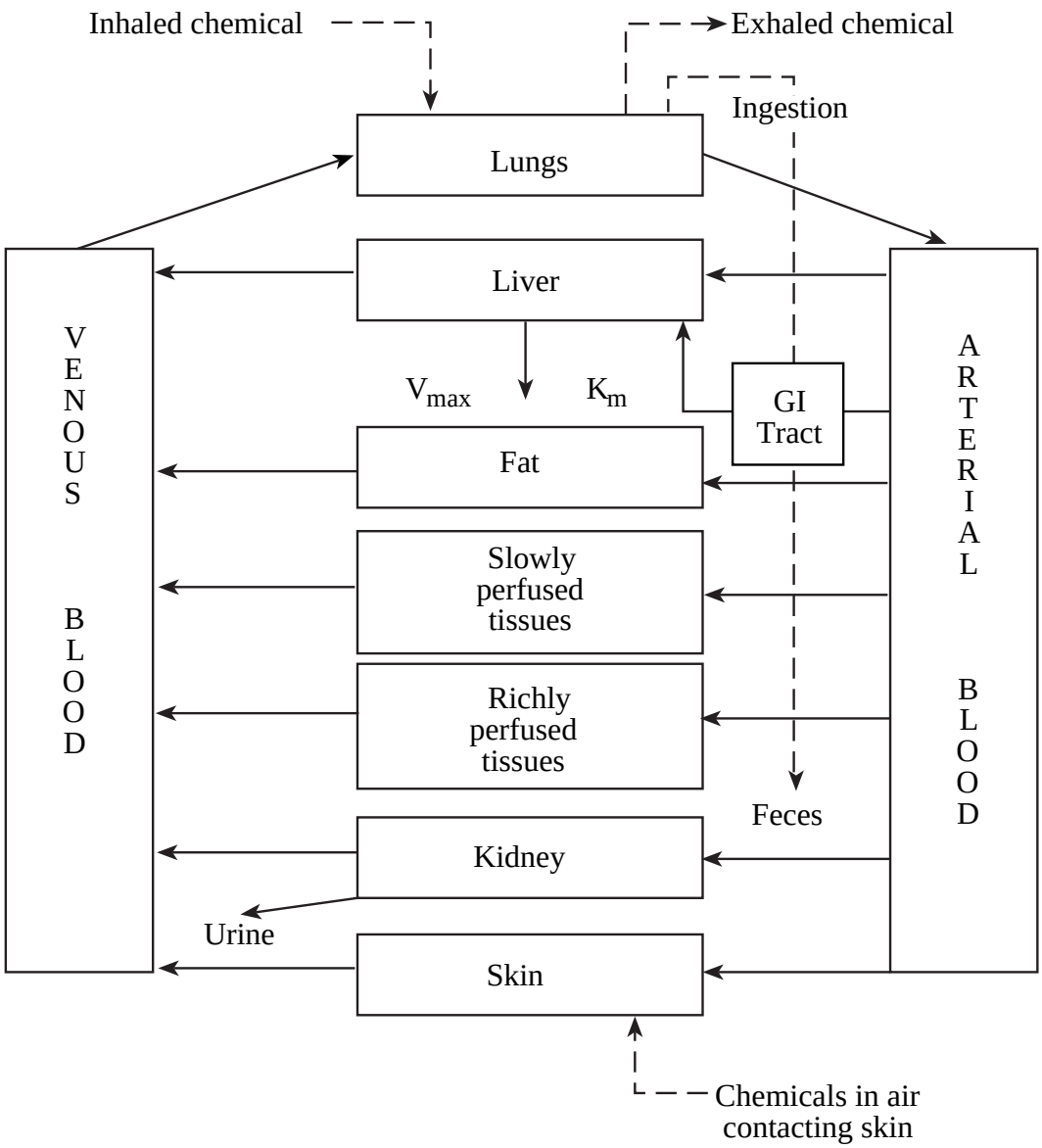
No PBPK models exist for ethion. Toxicokinetic information is insufficient for modeling.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

The pharmacokinetics of ethion have not been extensively studied. Ethion appears to be rapidly absorbed by the oral route. It is less well absorbed by the dermal route, but absorption may be prolonged as a consequence of using the epidermis as an intermediate storage depot (Feldman and Maibach 1974;

Figure 2-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Mosha et al. 1990b). Ethion is a small, lipophilic molecule and would be expected to be absorbed rapidly across cell membranes. Ethion is absorbed by passive diffusion from the gut, lungs, and skin to the blood. Ethion is desulfurated in the liver to its active metabolite, ethion monoxon. Some ethion monoxon and ethion can be inactivated by plasma cholinesterase or erythrocyte and neural acetylcholinesterase, but based on total esterase activity in the body, the liver is probably the major site of metabolism. The toxicity of a given dose of ethion depends on how rapidly neural acetylcholinesterase is inhibited; if this occurs before metabolic processes can reduce the blood level of ethion and ethion monoxon, significant toxicity will take place.

The reversibility of the reaction between ethion monoxon and neural acetylcholinesterase has not been studied. Based on studies with other diethyl organophosphates, it is probable that recovery of activity will depend on *de novo* synthesis of acetylcholinesterase rather than spontaneous reactivation (Ecobichon 1991).

2.4.2 Mechanisms of Toxicity

Ethion exerts its toxicity by inhibiting the neural acetylcholinesterase enzyme. Ethion is converted in the liver to ethion monoxon, a chemical form with an electrophilic phosphorus that is predisposed to nucleophilic attack. One potential nucleophile is the serine hydroxyl group located at the active site of acetylcholinesterase. The result of this reaction is a diethoxyphosphorylated acetylcholinesterase molecule. Over a time period of minutes to hours, a phenomenon known as “aging” can occur, whereby the diethoxyphosphorylated acetylcholinesterase molecule undergoes a spontaneous dealkylation, resulting in a monoethoxyphosphorylated acetylcholinesterase molecule, which is resistant to hydrolysis of the oxygen-phosphorus bond that would result in the regeneration of function of the enzyme. (The influence of the “aging” phenomenon on therapeutic interventions is discussed in section 2.11.3.) Neither the monoethoxyphosphorylated nor the diethoxyphosphorylated forms of acetylcholinesterase are capable of hydrolyzing acetylcholine. If this enzyme is inhibited, acetylcholine accumulates in the synapse and can interfere with neuron functioning. The parasympathomimetic consequences include lacrimation, perspiration, miosis, nausea, vomiting, diarrhea, excessive bronchial secretions, bradycardia, increased salivation, and increased urinary frequency and incontinence. Effects on motor nerve fibers in the skeletal muscles can include muscle fasciculations, cramps, muscle weakness, and flaccidity. Effects on cholinergic synapses in the central nervous system result in drowsiness, fatigue, mental confusion, headache, convulsions, and coma.

The nervous system can accept a certain amount of acetylcholinesterase inhibition without overt toxic effects. In humans and animals, toxic signs are generally not seen until at least 20% of this enzyme (erythrocyte acetylcholinesterase used as a marker) has been inhibited (Ecobichon 1991). In an animal study, brain acetylcholinesterase after a 2-year inhalation exposure to another organophosphate, dichlorvos, was inhibited more than 90% compared to control animals (Blair et al. 1976), yet signs of cholinergic overstimulation were not observed. With ethion and other organophosphate compounds, the best predictor of toxicity is not necessarily the actual percentage inhibition of acetylcholinesterase, but rather how rapidly this inhibition has occurred. Rapid inhibition does not give the nervous system time to adapt to acetylcholinesterase inhibition. This adaptation appears to involve desensitization and down-regulation of muscarinic receptors (Fitzgerald and Costa 1993).

There is no information available suggesting that the mechanism of toxicity of ethion is different between children and adults. Symptoms of toxicity in a 6-month-old boy poisoned by ethion (Comstock et al. 1967) were similar to those seen in adults acutely intoxicated by other organophosphates.

2.4.3 Animal-to-Human Extrapolations

Rats, dogs and goats all show clinical signs similar to those of humans after acute exposure to high doses of ethion. Information is insufficient to make any extrapolations from animal toxicokinetics to humans.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

Ethion is an organophosphorus insecticide that has been in use in the United States and elsewhere since the mid-1960s. Like other insecticides in this class, ethion is not only extremely toxic to insects, but also can be toxic to humans if high enough doses are received. The toxicity of ethion results from its inhibition of neural acetylcholinesterase. This enzyme is necessary to hydrolyze acetylcholine and terminate its action at synapses and ganglionic and neuromuscular junctions. The clinical signs of ethion toxicity are the result of overstimulation of the parasympathetic autonomic nervous system, somatic nerve fibers, and cholinergic pathways in the brain. After acute exposure to high concentrations of ethion by any route, signs such as lacrimation, perspiration, miosis, nausea, vomiting, diarrhea, bronchial secretion, dyspnea, increased salivation, and urinary frequency and incontinence can result from

overstimulation of the parasympathetic autonomic nervous system. The actions of ethion at neuromuscular junctions can result in muscle fasciculations (especially in fine facial muscles), cramps, muscle weakness, and paralysis. Ethion can also act in the central nervous system to produce drowsiness, fatigue, mental confusion, headache, convulsions, coma, and depression of respiratory centers in the brain.

There is limited information on the toxicity of ethion to humans. The potential hazards of this chemical were well known before it came into use because of experience with other organophosphorus compounds. Exposure to levels of ethion high enough to cause clinical symptoms of organophosphorus poisoning has been very rare in the United States. Clinical and biochemical signs of ethion toxicity in humans can be reproduced in animals. The metabolites of ethion are polar compounds that are excreted into the urine; thus, no potential for bioaccumulation exists. Laboratory studies in animals have not shown adverse reproductive or adverse developmental effects at doses that did not cause maternal toxicity. Ethion exposure has not been associated with organophosphate-induced delayed neurotoxicity (OPIDN) in humans and did not cause this condition in the preferred test species, the domestic hen.

Ethion has tested negative for mutagenicity in a number of *in vitro* test systems. Evaluation using *in vivo* test systems is limited to a single positive test for sister chromatid exchange in chickens (Bhunya and Jena 1994). Two-year oral exposure studies with ethion in rats and mice showed no evidence of carcinogenicity. Ethion has not been assessed for potential carcinogenicity in humans by the DHHS, the IARC, or the EPA.

The most likely population to be exposed to ethion is pesticide applicators. Exposure occurs during and/or after pesticide application. The National Institute of Occupational Safety and Health (NIOSH) recommends that ethion concentrations in workplace air not exceed 0.4 mg/m^3 for a 10-hour time-weighted average (TWA). Health effects could occur in workplaces if proper industrial hygiene and safety precautions are not followed. The exposure of the general population to ethion appears to be very low. Ethion has not been detected in drinking water in the United States and rarely detected in outdoor air (only at agricultural sites). Monitoring of the food supply by the U.S. Food and Drug Administration (FDA) and other government agencies has detected ethion, but levels are very rarely above tolerance levels set by the EPA. Thus, the risk of adverse health effects in the general population from ethion exposure appears to be negligible.

For people living near hazardous waste sites, the potential for adverse health effects would depend on the amount of ethion to which they were exposed. Ethion has been detected in at least 9 of the 1,577 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2000). However, the number of sites evaluated for ethion is not known. The most likely routes of exposure for people living near hazardous waste sites would be by breathing ethion-contaminated air, drinking ethion-contaminated water, or skin contact with ethion-contaminated soil. Monitoring of the air, drinking water, and soil levels of ethion at these sites is necessary to predict the possibility of adverse health effects.

Issues relevant to children are explicitly discussed in Sections 2.7, Children's Susceptibility, and 5.6, Exposures of Children.

Minimal Risk Levels for Ethion.

Inhalation MRLs.

No MRLs have been derived for inhalation exposure to ethion. No studies in humans on the effects of inhalation exposure to ethion were identified. The only animal study located (Fieser 1983 as cited in EPA 1989d) did not establish effect levels for neurological effects.

Oral MRLs.

- An MRL of 0.002 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to ethion. This MRL is also applicable to acute-duration (14 days or less) oral exposure to ethion.
- An MRL of 0.0004 mg/kg/day has been derived for chronic-duration (365 days or more) oral exposure to ethion.

These MRLs are based on a NOAEL of 0.06 mg/kg/day for brain acetylcholinesterase activity observed in dogs (Bailey 1988). To derive the intermediate-duration oral MRL, the NOAEL was adjusted by a factor of 30, 3 for extrapolation of an animal study to humans and 10 for human variability. The purpose of this study (Bailey 1988) was to evaluate the toxicity of ethion administered orally to dogs for 13 weeks.

Groups of Beagle dogs (n=4/sex/group, 20–28 weeks old) received ethion (purity 93.4%) in the diet at target concentrations of 0, 0.5, 2.5, 25, and 300 ppm for 90 days. Food was available for 2 hours a day, water was available *ad libitum.* The average amount of ethion consumed was 0, 0.01, 0.06, 0.71, and 6.9 mg/kg/day for males and 0, 0.012, 0.07, 0.71, and 8.25 mg/kg/day for females. All dogs were observed twice daily for mortality and moribundity. Animals were observed once daily for clinical signs. Body weights were recorded during acclimation and quarantine, on day 0 (one day prior to initiation and during week 13. Clinical pathology parameters were evaluated for all dogs prior to initiation of treatment (day -16) and during weeks 5, 9, and 13 and included cholinesterase activities (plasma, erythrocyte, brain), hematology, and clinical chemistry. All surviving animals were sacrificed following the 13-week treatment period. Histopathological examination of the following tissues was conducted: lesions, brain (with medulla/pons, cerebellar cortex, and cerebral cortex), gallbladder, pituitary, thyroid (parathyroid), thymus, lungs, trachea, heart, bone (femur), salivary glands (mandibular), bone marrow (sternum), kidneys, uterus adrenals, liver, spleen, pancreas, testes (with epididymides), ovaries, aorta, esophagus, stomach, duodenum, jejunum, ileum, colon, cecum, rectum, urinary bladder, mesenteric lymph node, sciatic nerve, spinal cord (cervical, thoracic, lumbar), skin, mammary gland, and eyes.

One female dog in the 8.25 mg/kg/day group was sacrificed on day 90 (1 day before schedule). Clinical signs exhibited by this animal prior to sacrifice included emesis, dehydration, and thin body mass. All other animals survived until terminal sacrifice. In the highest dose group (6.9 mg/kg/day for males, 8.25 mg/kg/day for females) clinical signs included miosis (all animals), emesis (all animals), dehydration (3 males, 2 females), salivation (2 males, 2 females), and tremors (3 males, 4 females). Animals in this group appeared to be in generally poor condition at the end of the study. Erythrocyte acetylcholinesterase was inhibited at weeks 5 (94% M, 96% F), 9 (95% M, 93% F), and 13 (94% M, 93% F) in the highest dose groups, but not in any of the other groups. Mean percent brain acetylcholinesterase activity inhibition at termination was 64% in males and 61% in females at the highest dose. Male brain acetylcholinesterase was inhibited 23% at 0.71 mg/kg/day but no inhibition of brain acetylcholinesterase occurred in females at this dose. Plasma cholinesterase inhibition was dose-related in both males and females. No significant differences in absolute organ weights were observed between treated and control animals. No compound-related Histopathological effects were observed in any organ, including brain, sciatic nerve and spinal cord. The NOAEL for inhibition of brain acetylcholinesterase is 0.06 mg/kg/day.

This study was chosen for MRL derivation because it identifies both a NOAEL and LOAELs for inhibition of neural acetylcholinesterase, the target for ethion toxicity in humans. A study in albino rats

fed ethion for 93 days established a NOAEL for brain acetylcholinesterase inhibition of 1 mg/kg/day (Keller and Paynter 1958), which is higher than that used to derive the MRL. Neither erythrocyte nor brain acetylcholinesterase activities were inhibited in rats (up to 2 mg/kg/day) or mice (up to 1.25 mg/kg/day) receiving ethion in the diet for 6 or 12 months (Morrow et al. 1985a, 1985b).

This MRL should be protective against adverse health effects in individuals potentially exposed to ethion at hazardous waste sites. A study in volunteers (Palazzolo 1970) has determined the sensitivity of humans to the effects of ethion on blood cholinesterase activities. A group of six male volunteers were given ethion in corn oil solutions in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) of 0.05, 0.075, 0.1, and 0.15 mg/kg/day via gelatin capsule. Subjects received 0.05, 0.075, and 0.1 mg/kg/day for 3 weeks each and then 0.15 mg/kg/day for 3 days. No adverse clinical signs (blood pressure, pulse rate, pupil size, light reflex, eye accommodation, chest sound, muscle tone, knee jerk, tongue tremor and finger tremor) or effects on erythrocyte acetylcholinesterase were observed at any time during the study. Absorption of ethion by the volunteers was confirmed by a decrease in plasma cholinesterase levels. While no effect on plasma cholinesterase was observed at the 0.05 mg/kg/day dose level, a 16% decrease was seen in the 0.075 mg/kg/day group. Decreases of 23 and 31% were seen in the 0.1 and 0.15 mg/kg/day groups.

To derive the intermediate oral MRL, the NOAEL of the Bailey (1988) study for inhibition of brain acetylcholinesterase was adjusted by a factor of 10 for human variability and a factor of 3 for extrapolation of an animal study to humans. A factor of 3 was used for extrapolation rather than the full uncertainty factor of 10 because the results of the Palazzolo (1970) study indicated that dogs appear to be at least as sensitive to the neurological effects of ethion as humans when exposed to comparable doses.

The MRL value of 0.002 mg/kg/day for intermediate-duration oral exposure to ethion was extended to acute oral exposure based on the toxicokinetics of ethion. Cholinesterase inhibition occurs quickly and there are no indications of progressive inhibition over time at a given dose in either the Palazzolo (1970) study in humans or the Bailey (1988) study in dogs. A similar lack of progression of inhibition was seen in 2-year studies in rats and mice where brain and erythrocyte acetylcholinesterase and plasma cholinesterase were measured at 6-month intervals (Morrow et al. 1985a, 1985b). The toxicity database indicates no change in ethion toxicity over time (i.e., toxicity is dependent on the dose, not the duration of exposure). Because the toxicological effects of ethion are due to a series of repeated acute exposures, it is proposed that the intermediate-duration oral MRL should be protective for the acute exposure

duration. For chronic duration, an additional modifying factor of 5 was applied to protect against possible long-term effects, seen in structurally-related cholinesterase inhibitors, which might be the result of mechanisms other than cholinesterase inhibition, and to protect against possible susceptibility in children. Application of this factor resulted in a chronic-duration oral MRL of 0.0004 mg/kg/day.

Death. No studies were located describing death in humans after exposure to ethion. However, without prompt medical attention, it is likely that a 6-month-old boy who ingested 15.7 mg/kg ethion from a contaminated milk bottle would have died (Comstock et al. 1967).

Animal studies show that ethion is highly toxic by the oral route; reported LD_{50} values in the rat range from 21 to 191 mg/kg. Deaths have also occurred by the inhalation and dermal route in animal studies. Reported LD_{50} values for dermal exposure in rats range from 62 to 838 mg/kg while inhalation LC_{50} values range from 0.45 to 2.31 mg/m^3 (Gaines 1969; Fieser 1983 as cited in EPA 1989d).

Systemic Effects. Ethion exerts its toxicity by inhibiting neural acetylcholinesterase in the central and peripheral nervous systems. Some of these effects occur in different organ systems but are ultimately the result of neurological effects. In animal studies where tissues have been examined histopathologically, ethion does not appear to have direct effects on organ systems.

Respiratory Effects. Respiratory effects have been reported in humans after oral exposure to ethion. A 6-month-old boy who accidentally ingested 15.7 mg/kg ethion from a contaminated milk bottle presented with diaphragmatic respiration with shallow excursions and intercostal retraction (Comstock et al. 1967). Respiratory rate was 60/minute. Auscultation revealed generalized rales and rhonchi and inspiratory and expiratory wheezes; all signs of increased secretions in the respiratory tract. Symptoms appeared one hour following ingestion and were treated with atropine and pralidoxime. Approximately 5 hours after ingestion respiratory arrest occurred and mechanical ventilation was necessary for the next 3 hours. It is not known if respiratory arrest was due to muscular paralysis. The respiratory effects seen in this case are consistent with cholinergic overstimulation caused by ethion.

Longer-term oral exposure at lower doses in animal experiments did not show effects on the respiratory system. Histopathological examination of the lungs and trachea revealed no treatment-related lesions several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Cardiovascular Effects. Tachycardia was reported in a 6-month-old boy who accidentally ingested 15.7 mg/kg ethion (Comstock et al. 1967).

Blood pressure and pulse rate were measured in a group of 6 male volunteers (age range, 23–43 years) who were given ethion in corn oil solutions in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) via gelatin capsule (Palazzolo 1970). Doses were 0.05 mg/kg/day for 21 consecutive days, 0.075 mg/kg/day for the next 21 days, 0.1 mg/kg/day for the next 21 days, and 0.15 mg/kg/day for the next 3 days. Controls (n=4; age range, 22–40 years) received gelatin capsules containing corn oil. No differences were noted between the control and test groups, or between individual pre-treatment, treatment, or post-treatment results for blood pressure or pulse rate.

Studies on the effects of ethion on electrical activity of the heart were not found in the literature. Histopathological examination of the heart and aorta revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Gastrointestinal Effects. Gastrointestinal effects reported in a 6-month-old boy who accidentally ingested 15.7 mg/kg ethion (Comstock et al. 1967) included frothy saliva 1 hour after ingestion and a watery bowel movement at 90 minutes. Bowel sounds were hyperactive and an episode of emesis occurred 5 hours after ingestion.

Diarrhea was reported in Sprague-Dawley rats exposed to ethion by gavage at 10 mg/kg in females and 100 mg/kg in males (Selim 1985a). Severe signs of neurotoxicity (convulsions) were also present. The gastrointestinal effects seen in both cases are consistent with cholinergic overstimulation of the gastrointestinal tract.

Histopathological examination of gastrointestinal tissues (esophagus, stomach, duodenum, jejunum, ileum, colon, cecum, rectum) revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Hematological Effects. Significant hematological effects have not been observed in two cases of human exposure to ethion. In a poisoning case of a 6-month-old boy who accidentally ingested 15.7 mg/kg

ethion, hematocrit, hemoglobin level, and RBC and platelet counts were normal (Comstock et al. 1967). WBC counts were initially slightly depressed but returned to normal after one day.

Similar results were seen for intermediate-duration oral exposure in a group of 6 male volunteers (age range, 23–43 years) who were given ethion in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) via gelatin capsule (Palazzolo 1970). Doses were 0.05 mg/kg/day for 21 consecutive days, 0.075 mg/kg/day for the next 21 days, 0.1 mg/kg/day for the next 21 days, and 0.15 mg/kg/day for the next 3 days. Controls (n=4; age range, 22–40 years) received gelatin capsules containing corn oil. Blood studies (hemoglobin concentration, hematocrit, RBC and total and differential leukocyte counts) were performed on days -15 and -1 of the pretreatment period, at the end of each of the 4 treatment periods, and after a 19-day recovery period after dosing ended. No differences were noted between the control and test groups, or between individual pre-treatment, treatment, or post-treatment results for any of the parameters.

Hematological parameters (leukocyte count, erythrocyte count, hemoglobin, corrected leukocyte count, hematocrit, platelet count, differential leukocyte count) were unaffected by treatment in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Musculoskeletal Effects. Oral exposure to ethion can result in muscle tremor and fasciculations. These effects are discussed under Neurological Effects.

The effect of oral exposure to ethion on muscle tone was assessed in a group of 6 male volunteers (age range, 23–43 years) who were given ethion in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) via gelatin capsule (Palazzolo 1970). Doses were 0.05 mg/kg/day for 21 consecutive days, 0.075 mg/kg/day for the next 21 days, 0.1 mg/kg/day for the next 21 days, and 0.15 mg/kg/day for the next 3 days. Controls (n=4; age range, 22–40 years) received gelatin capsules containing corn oil. Muscle tone was assessed at the beginning and end of each treatment period. No differences were noted between the control and test groups or between individual pre-treatment, treatment, or post-treatment results.

Histopathological examination of the bone and skeletal muscle revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to ethion.

Histopathological examination of the liver revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to ethion.

Histopathological examination of endocrine tissues (pituitary, thyroid, parathyroid, thymus and adrenals) revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Renal Effects. Proteinuria and increased urinary WBC counts were observed in a severely intoxicated 6-month-old boy who accidentally ingested 15.7 mg/kg ethion (Comstock et al. 1967).

An increased incidence of orange-colored urine was observed in pregnant New Zealand rabbits receiving 2, 4, or 9.6 mg/kg/day during Gd 6–18 (Hoberman et al. 1983b). This effect was not observed at 0.6 mg/kg/day. The urine was not examined by chemical analyses.

Histopathological examination of the urinary bladder and kidneys revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to ethion.

Histopathological examination of the skin revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to ethion.

Histopathological examination of the eyes revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to ethion.

An unspecified body weight decrease occurred in New Zealand rabbit does receiving 2.4 mg/kg/day ethion via gavage over Gd 6–18. No effect on body weight was seen at 0.6 mg/kg/day (Hoberman et al. 1983b). No effect was observed on body weight in male and female dogs receiving #0.71 mg/kg/day in the diet for 13 weeks (Bailey 1988).

Body weight decreases accompanied by reduced food consumption have been observed in New Zealand rabbit dams receiving 9.6 mg/kg/day ethion via gavage over Gd 6–18 and in male and female Beagle dogs receiving 6 and 8.25 mg/kg/day, respectively, in feed (Bailey 1988).

Immunological and Lymphoreticular Effects. No studies were located regarding immunological/lymphoreticular effects in humans after exposure to ethion.

Histopathological examination of immunological/lymphoreticular tissues (mesenteric lymph node, thymus, bone marrow) revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Neurological Effects. Ethion exerts its toxic effects in humans and animals by inhibiting neural acetylcholinesterase. This enzyme is present at cholinergic synapses throughout the central and peripheral nervous systems and is responsible for hydrolyzing acetylcholine released from the pre-synaptic terminal. If this enzyme is inhibited, acetylcholine accumulates in the synapse, resulting in increased firing of the post-synaptic neuron or increased neuroeffector activity. The consequences of increased cholinergic activity in the parasympathetic autonomic nervous system (muscarinic receptors) can include increased salivation, lacrimation, perspiration, miosis, nausea, vomiting, diarrhea, excessive bronchial secretions, bradycardia, frequent micturition, and incontinence. The effects of increased neuroeffector activity on skeletal muscles (nicotinic receptors) can include muscle fasciculations, cramps, muscle weakness, and depolarization-type paralysis. Effects on cholinergic synapses in the

central nervous system (predominantly muscarinic) can result in drowsiness, fatigue, mental confusion, headache, convulsions, and coma. These classical symptoms of organophosphate neurotoxicity increase in severity and rapidity of onset in a dose-dependent manner (Ecobichon 1991).

Acetylcholinesterase is also present in erythrocytes where it is referred to as erythrocyte acetylcholinesterase. Both forms of acetylcholinesterase are produced by the same gene (Taylor et al. 1993). In *in vitro* assays, erythrocyte and neural acetylcholinesterase are inhibited to roughly the same extent by exposure to organophosphate compounds with insecticide activity (Hayes 1982). Measurement of erythrocyte acetylcholinesterase is used as a surrogate of the inhibition of neural acetylcholinesterase. A cholinesterase capable of hydrolyzing acetylcholine is also produced by the liver and circulates in the blood. This enzyme, called plasma cholinesterase, is also inhibited by ethion and other organophosphates and can be used as a marker for exposure. The endogenous substrate of this enzyme is unknown. Experiments in both humans and animals show that this enzyme is inhibited by ethion at lower levels of exposure than required to inhibit neural or erythrocyte acetylcholinesterase (Bailey 1988).

A case study of a 6-month-old boy who accidentally ingested 15.7 mg/kg ethion from a contaminated milk bottle illustrates the toxic neurological effects of ethion (Comstock et al. 1967). Symptoms appeared one hour following ingestion. The child awoke crying and choking on frothy saliva. He was unable to control his head and limbs and subsequently had a watery bowl movement and became limp. Occasional twitching movements of the hands and around the mouth were noted. Upon admission to the hospital, he was slightly cyanotic with a generalized flaccid paralysis and areflexia. Respiration was increased (60/minute) as was heartbeat (200/minute). Pupils were pinpoint and nonreactive to light, and eye movements were purposeless. Salivation was excessive but not copious. Respiration was diaphragmatic with shallow respiratory excursions and intercostal retraction. Generalized rales and rhonchi and inspiratory and expiratory wheezes were noted. The liver and spleen were palpable. Bowel sounds were hyperactive. There were no abnormal heart sounds. Treatment with atropine and pralidoxime was started immediately. Approximately 5 hours after ingestion, respiratory arrest occurred and mechanical ventilation was necessary for the next 3 hours. Laboratory and roentgenologic studies showed protein in the urine and increased WBC in the urine. Serum WBC count was decreased and treated with atropine and pralidoxime. Treatment with atropine and pralidoxime continued for 5 days until symptoms ceased. Follow-up examinations after 1 week, 1 month, and 1 year indicated that a complete recovery was made by this patient.

2. HEALTH EFFECTS

A study with male volunteers established oral levels of exposure to ethion that had no adverse effect in humans (Palazzolo 1970). Male volunteers (n=6; age range, 23-43 years) were given ethion in corn oil solutions in three divided doses (9:00 a.m., noon, and 5:00 p.m.) of 0.05, 0.075, 0.1, and 0.15 mg/kg/day via gelatin capsule. Controls (n=4; age range, 22-40 years) received gelatin capsules containing corn oil. Medical histories and baseline plasma cholinesterase and erythrocyte acetylcholinesterase activities were determined prior to the start of the study (days -15, -11, -8, -4, and -1). Blood samples were taken prior to dose administration. Subjects received 0.05, 0.075, and 0.1 mg/kg/d for 3 weeks each. Cholinesterase determinations were conducted on days 1, 3, 7, 14, and 21 for these dose groups. Subjects received 0.15 mg/kg for 3 days and cholinesterase determinations were made on days 1 and 3. A 19-day recovery period followed, and cholinesterase determinations were made on days 7, 12, and 19. At the beginning and end of each treatment period, pupil size, light reflex, eye accommodation, muscle tone, knee jerk, tongue tremor, and finger tremor were measured.

No effect on erythrocyte acetylcholinesterase was observed at any time during the human exposure study. No effect on plasma cholinesterase were observed at the 0.05 mg/kg/day dose level. Statistically significant decreases from pretreatment values were observed for all plasma cholinesterase determination periods during the 0.075, 0.1, and 0.15 mg/kg/day treatment periods. A significant 16% decrease in plasma cholinesterase activity was seen in the 0.075 mg/kg/day group. When compared to pretreatment values, decreases of 23 and 31% were seen in the 0.1 and 0.15 mg/kg/day groups, respectively. A partial recovery of plasma cholinesterase levels were seen after 7 days of recovery, while a complete recovery was seen after 12 days. No clinical signs of adverse neurological effects were observed.

Severe neurological effects have also been observed in rats after a single oral exposure to ethion. Male Sprague-Dawley rats receiving 100 mg/kg ethion by gavage had cholinergic signs including salivation, tremors, nose bleeding, urination, diarrhea, and convulsions (Selim 1985a). Female rats exhibited these same signs at a 10-fold lower dose (10 mg/kg). In another acute oral exposure to ethion, groups of pregnant Sprague-Dawley rats (n=25) were administered ethion via gavage at doses of 0,0.2,0.6, and 2.5 mg/kg from Gd 6 to 15 (Hoberman et al. 1983a). An increased incidence of hyperactivity was observed in dams in the 2.5 mg/kg group. In a test of ethion in chickens for potential to cause delayed neurotoxicity, an oral dose of 2,792 mg/kg caused neither clinical or histopathological signs of this condition (Roberts et al. 1986).

In longer-term experiments in animals, groups of Sprague-Dawley rats (n=80/sex/group) fed diets resulting in ethion consumption of 0, 0.1, 0.2, and 2 mg/kg/day, no effect on erythrocyte acetylcholinesterase was observed at 6, 12, or 18 months (Morrow 1985a). Significant neurological effects were observed in dogs receiving higher doses of ethion (Bailey 1988). Groups of dogs (n=4/sex/group) received ethion in the diet for 90 days, the average consumed was 0, 0.01, 0.06, 0.71, and 6.9 mg/kg/day for males and 0, 0.012, 0.07, 0.71, and 8.25 mg/kg/day for females. Clinical signs included ataxia, emesis, miosis, and tremors in the high-dose groups. Ethion inhibited brain and erythrocyte acetylcholinesterase activity in a dose-related manner. A reduction of 23% in brain acetylcholinesterase was observed in males at 0.71 mg/kg/day and 64% at 6.9 mg/kg/day; no effect was seen at 0.07 and 0.012 mg/kg/day. Plasma cholinesterase activity was inhibited in all groups except the low-dose males and females and was dose-related. No compound-related histopathological changes were observed in nervous system tissues (brain [with medulla/pons, cerebellar cortex, and cerebral cortex], sciatic nerve, spinal cord [cervical, thoracic, lumbar]).

In chronic-duration experiments, a 3-generation reproduction study in albino rats that consumed ethion in feed at 0, 0.1, 0.2, and 1.25 mg/kg/day, showed that plasma cholinesterase was inhibited in F_1 and F_2 females in the high-dose group. No effect was observed on erythrocyte acetylcholinesterase in any group (Enloe and Salamon 1985). In 2-year carcinogenicity bioassay experiments, no effect on erythrocyte acetylcholinesterase was observed at daily exposures of #2 mg/kg/day in rats and 1.12 mg/kg/day in mice (Morrow 1985a, 1985b).

Inhibition of brain acetylcholinesterase was observed in rabbits after dermal exposure to ethion for 21 days at 1 mg/kg/day, (Weiner 1985a, 1985b as cited in EPA 1989d). The NOAEL in these studies was 0.8 mg/kg/day.

Histopathological examination of nervous system tissues (brain, spinal cord, peripheral nerve) showed no treatment-related effects in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Reproductive Effects. In a 3-generation reproduction study, ethion was administered to F_0, F_1, and F_2 male (n=15) and female (n=30) rats in the diet at concentrations of 0, 0.1, 0.2, and 1.25 mg/kg/day. No effect on reproduction was observed (Enloe and Salamon 1985). Indices measured were: mating index (number of copulations/number of estrus cycles utilized), fertility index (number of

pregnancies/number of copulations), gestation (number of parturitions/number of pregnancies), female fertility (number of pregnancies/number of females mated), and male fertility (number of sires/number of males mated).

Histopathological examination of reproductive tissues (uterus, ovaries, testes) revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Developmental Effects. Three studies examining the effects of ethion on development are available. Groups of pregnant Sprague-Dawley rats (n=25) were administered ethion via gavage at doses of 0, 0.2, 0.6, and 2.5 mg/kg from Gd 6 to 15 (Hoberman et al. 1983a). Dams were observed and skeletal examinations were performed on the fetuses. Fetuses from the 2.5 mg/kg group had an increased incidence of delayed ossification of pubes. Groups of pregnant New Zealand rabbits (n=17) received ethion via gavage at doses of 0, 0.6, 2.4, and 9.6 mg/kg from Gd 6 to 18 (Hoberman et al. 1983b). Does were observed for clinical signs. Maternal toxicity was noted, does in the 2.4 and 9.6 mg/kg/day groups had an increased incidence of orange-colored urine and decreased body weights (not specified). Food consumption was also reduced in the 9.6 mg/kg/day females. Fetuses in the 9.6 mg/kg/day group had an increased incidence of fused sterna centra. In a 3-generation reproduction study, ethion was administered to F_0, F_1, and F_2 male (n=15) and female (n=30) rats in the diet at concentrations of 0, 0.1, 0.2, and 1.25 mg/kg/day. No effect was observed on pup viability, survival, body weight, or structural development (Enloe and Salamon 1985).

Genotoxic Effects. Ethion has shown no evidence of genotoxicity in several *in vitro* tests (see Table 2-3). Ethion was negative in tests for point mutations (Kada et al. 1974; Waters et al. 1980), DNA repair (Shirasu et al. 1976; Waters et al. 1980), recombination (Waters et al. 1980), sister chromatid exchange (Sobti et al. 1982), and unscheduled DNA synthesis (Waters et al. 1980). An increase in the frequency of sister chromatid exchanges was observed in white Leghorn chicks following a single oral (2 mg/kg) or intraperitoneal (20 mg/kg) dose of ethion (Bhunya and Jena 1994). No other *in vivo* tests of ethion genotoxicity were located.

Cancer. In 2-year carcinogenicity bioassays, groups of Sprague-Dawley rats (n=80/sex/group) receiving diets containing ethion at concentrations of 0, 0.1, 0.2, and 2 mg/kg/day had similar tumor incidences (Morrow 1985a). Similar results were observed in mice receiving 0, 0.113, 0.225, and

Table 2-3. Genotoxicity of Ethion *In Vitro*

System	End points	Results		References
		With activation	Without activation	
Prokaryotes:				
S. typhimurium (Strains TA 98, TA 100, TA 1535, TA 1537, TA 1538)	Point mutation	All negative	All negative	EPA 1989a,b,c,d; Haworth 1984
S. typhimurium (Strains TA 1535, TA 1536, TA 1537, TA 1538)	Point mutation	No data	All negative	Kada et al. 1974
S. typhimurium (Strains TA 100, TA 1535, TA 1537, TA 1538)	Point mutation	All negative	All negative	Waters et al. 1980
E. coli (Strain WP2 (urvA$^-$))	Point mutation	All negative	All negative	Waters et al. 1980
E. coli (Strains W3110, P3478)	DNA repair	No data	All negative	Waters et al. 1980
B. subtilis (Strains H17 , M45)	DNA repair	No data	All negative	Waters et al. 1980
B. subtilis (Strains H17, M45)	DNA repair	No data	All negative	Shirasu et al. 1976
S. cerevisiae (Strain D3)	Recombination	Negative	Negative	Waters et al. 1980
Eukaryotes				
Human lymphoid cells (LAZ-007)	Sister chromatid exchange	No data	Negative	Sobti et al. 1982
Human fetal lung fibroblasts (WI-38)	Unscheduled DNA synthesis	No data	Negative	Waters et al. 1980

1.2 mg/kg/day (Morrow 1985b). Ethion has not been classified for carcinogenicity by DHHS, IARC or EPA.

2.6 ENDOCRINE DISRUPTION

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997c). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans or animals after exposure to ethion. No *in vitro* studies were located regarding endocrine disruption by ethion.

2.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 5.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per

kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

The toxicological database for the effects of ethion on humans is sparse. Ethion is not used in the home, and no toxicological studies on individuals likely to have significant exposure (formulators and applicators) are available in the literature. One well documented case report of a poisoning incident in an infant has been published (Comstock et al. 1967). The only other human study located at this time is an unpublished study that established no-effect levels for oral exposure to ethion in adult males (Palazzolo 1970).

The effects of ethion have not been thoroughly studied in children, but they would likely experience the same health effects seen in adults exposed to ethion. Effects observed in an infant accidentally poisoned by ethion (Comstock et al. 1967) were similar in onset, severity, and duration to those seen in adults poisoned by other organophosphate insecticides (Ecobichon 1991). Symptoms observed in the infant (muscular twitching, lack of coordination, flaccid paralysis and areflexia, excessive salivation, pinpoint pupils, watery bowel movement, proteinurea, increased urinary white cell count, emesis, tachycardia) are classic symptoms of organophosphate poisoning in adults. Five days of treatment with atropine and pralidoxime were necessary before recovery; this is comparable to clinical courses seen in poisoned adults. Recovery appeared to be complete at a 1-year follow-up; this is also the case in adults (assuming that the organophosphate does not cause delayed neurotoxicity). These same effects are seen in animal studies. In the only animal study that directly compared weanling and adult animals (Brodeur and DuBois 1963), the LD_{50} for weanling male Holtzman rats after intraperitoneal injection was 100 mg/kg (95% confidence limits 92–109). For adult male Holtzman rats, the LD_{50} was 128 mg/kg (95% confidence limits 110–149). This indicates that weanlings may be slightly more susceptible to the lethal effects of ethion.

Specific information on whether children differ from adults in their susceptibility to the effects of ethion is not available. Animal studies do not provide any further information. Two areas of concern for exposure of children to ethion and other organophosphates have been identified. First, the target tissue for ethion is the peripheral and central nervous system. The central nervous system continues to develop after birth and it is not known if, or at what point, neural acetylcholinesterase inhibition can affect this process and result in permanent effects. It is possible that effects could occur with inhibition levels that

cause no clinical effects. Secondly, infants and children receive approximately 2–3 times more ethion in their diets per unit body weight than adults due to higher consumption of fruits and fruit drinks (See Chapter 5).

Ethion has not caused teratogenic effects in animal models (rats, rabbits), although some skeletal abnormalities have been reported (delayed ossification, fused sterna centra). These effects occurred at maternally toxic doses (Hoberman et al. 1983a, 1983b). Observation of the offspring after birth to maturity was not performed. No developmental effects were observed in progeny in a 3-generation rat reproduction study (Enloe and Salamon 1985). Ethion has not been tested in *in vitro* developmental systems.

The pharmacokinetics of ethion are not well understood in animal models, and no information is available on human adults or children. Studies in animals are limited by the fact that chemical characterization of radiolabeled ethion and its metabolic products in tissues was not performed. Ethion and its active metabolite ethion monoxon are highly lipophilic molecules so there should be no significant barrier to crossing the placenta. No studies have been done in animal models to confirm whether this occurs. Similarly, passage into breast milk is also possible. This has been examined in animal models. Radioactivity derived from labeled ethion was present in goat milk after oral exposure (Jobsis and Zeitlow 1985); however, the chemical identity of the radioactivity was not determined. Unchanged ethion (the monoxon was not measured) was detected in goat milk after oral (1.4% of administered activity) and dermal (0.04–0.05% of administered activity) exposure to ethion (Mosha et al. 1990b).

The toxicity of ethion is determined by two biotransformations, a desulfuration by a cytochrome P-450 enzyme yielding the active metabolite ethion monoxon and detoxication by an ester cleavage catalyzed by an esterase. Some, but not all, P-450 isozymes are regulated differently during development than during adulthood (Leeder and Kearns 1997); without knowing the specific isozymes involved in ethion metabolism it is impossible to predict whether its metabolism would vary developmentally. Comparisons of juvenile and adult animal toxicokinetics have not been made. There are no PBPK models for ethion available for children, adults, or animal models. The toxicokinetic database is insufficient for modeling purposes.

There is no evidence that the mechanism of ethion toxicity is different between children and adults. The symptoms of severe neural acetylcholinesterase inhibition observed in a 6-month-old infant were similar to those seen in adult poisonings with other organophosphate insecticides. The acetylcholinesterase molecule is believed to be the same at all stages of development (there is no evidence for a "fetal" acetylcholinesterase).

The biomarkers of exposure and effect (plasma cholinesterase and erythrocyte acetylcholinesterase in blood) are similar between adults and children. However, less is known about how much inhibition of these enzymes is associated with health effects in children than in adults. Information is not available for infants and children on the relationship between dietary intake and the activity of blood cholinesterases.

Interactions of ethion with other chemicals have not been reported in children or adults. There is not enough information from animal studies to determine if juvenile animals have unique interactions. As with adults, it is reasonable to expect interactions with compounds that inhibit acetylcholinesterases.

Methods for reducing the toxic effects of ethion in children are similar to those used in adults. Doses of the antidotes atropine and pralidoxime, adjusted for body weight, have been shown to be effective treatment for acute poisoning (Comstock et al. 1967).

There is no information on whether parental exposure to ethion can cause transgenerational effects in children. No effects were noted in a 3-generation rat reproduction study (Enloe and Salamon 1985). Ethion has tested negative for genotoxicity in a number of *in vitro* tests.

2.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC

1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to ethion are discussed in Section 2.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by are discussed in Section 2.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.10, Populations That Are Unusually Susceptible.

2.8.1 Biomarkers Used to Identify or Quantify Exposure to Ethion

Ethion at high doses will cause clinical symptoms of organophosphate toxicity, such as miosis, tremor, increased salivation, lacrimation, and respiratory distress. If these symptoms occur together and the individual has recently been in contact with pesticides containing ethion, it is highly likely that exposure to ethion has occurred.

Exposure to ethion can also be confirmed by blood tests; however, these tests are not specific for ethion. Ethion can inhibit the activity of two enzymes in the blood, plasma cholinesterase and erythrocyte acetylcholinesterase. Plasma cholinesterase is more sensitive to inhibition by ethion than erythrocyte acetylcholinesterase in both humans and animals. Plasma cholinesterase activity recovers more rapidly from inhibition than erythrocyte acetylcholinesterase because of the higher turnover rate of plasma cholinesterase proteins compared to erythrocytes. Exposures that occurred two weeks or more before testing probably would not be reflected in an inhibition of plasma cholinesterase. Because of the human variability in activity of these enzymes, follow-up determinations showing a rise back to a constant activity are more reliable evidence than a single determination that exposure has taken place. Many other organophosphate and carbamate insecticides can cause inhibition of blood cholinesterases.

Ethion has been detected in saliva of pest control applicators (Nigg et al. 1993). Diethyl phosphate metabolites of ethion were also detected in the workers' urine. The correlation between urinary metabolites and saliva ethion was 0.55, indicating that saliva ethion was not a good predictor of absorbed ethion. The authors stated that mouth contamination may have influenced the results. Further development of this method may result in a specific biomarker of exposure for ethion.

2.8.2 Biomarkers Used to Characterize Effects Caused by Ethion

The toxic effects of ethion are caused by its inhibition of neural acetylcholinesterase in the peripheral and central nervous systems. This inhibition is reflected by the level of depression of erythrocyte acetylcholinesterase activity in the blood.

The nervous system can accept a certain amount of acetylcholinesterase inhibition without overt toxic effects. In humans and animals, toxic signs are generally not seen until at least 20% of this enzyme (measured as erythrocyte acetylcholinesterase) has been inhibited (Ecobichon 1991). Adaptation can also occur. In an animal study, brain acetylcholinesterase was inhibited 90% after a 2-year inhalation exposure to the organophosphate dichlorvos (Blair et al. 1976), yet no symptoms of cholinergic overstimulation were observed. With ethion and other organophosphate compounds, the best predictor of toxicity is not necessarily the actual percentage of inhibition of acetylcholinesterase, but rather how rapidly this inhibition has occurred. Rapid inhibition does not give the nervous system time to physiologically adapt to acetylcholinesterase inhibition. This adaptation appears to involve desensitization and down-regulation of muscarinic receptors (Fitzgerald and Costa 1993).

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.9 INTERACTIONS WITH OTHER CHEMICALS

Reports on specific interactions of ethion with other chemicals are limited. Ethion administered orally at 25 mg/kg in rats did not increase the lethality of 53.5 mg/kg of the organophosphate bromophos-ethyl (Muacevic 1973). Several of the other organophosphates tested (parathion, chlorfenvinphos) increased the toxicity of bromophos-ethyl in this study. Pretreatment with phenobarbital to induce cytochrome P-450 enzymes significantly reduced the lethality of ethion in Holtzman rats after intraperitoneal injection (LD_{50} without pretreatment, 25.9 mg/kg; with phenobarbital pretreatment, 302.6 mg/kg). However, lethality in CF_1 mice in the same study was unaffected by pretreatment with phenobarbital (DuBois and Kinoshita 1968).

The major interaction of concern for ethion would be with chemicals that have the same mechanism of action (i.e., organophosphate and carbamate pesticides). Simultaneous exposure to ethion and one of these chemicals could possibly have an additive effect on inhibition of neural acetylcholinesterase.

Whether a toxic interaction would occur with a particular chemical depends on how it affects the toxicokinetics of ethion. The toxicity of a given dose of ethion could conceivably be potentiated by interactions with chemicals that interfere with its detoxication; however, no such interactions have been reported. This effect has occurred with other organophosphates, e.g., the potentiation of malathion by the carboxylesterase inhibitor EPN (ethyl *p*-nitrophenyl benzenethiophosphonate) in rats and dogs (Frawley et al. 1957). Some chemicals can induce the synthesis of cytochrome P-450 enzymes (polysubstrate mixed function oxidases) in the liver (e.g., organochlorines). Whether this would increase or decrease the toxicity of ethion in humans is not known. While mixed function oxidases are responsible for the activation of ethion (via desulfuration), it is not known if they play any role in detoxication since specific metabolic pathways are unknown. For the same reason, interactions of ethion with inhibitors of mixed function oxidases cannot be predicted. These effects are species specific; induction decreased the lethality of ethion in rats but had no effect in mice (DuBois and Kinoshita 1968).

2.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to ethion than will most persons exposed to the same level of ethion in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of ethion, or compromised function of organs affected by ethion. Populations who are at greater risk due to their unusually high exposure to ethion are discussed in Section 5.7, Populations With Potentially High Exposures.

Individuals with impaired respiratory function or diseases of the central or peripheral nervous systems may be more susceptible to the effects of ethion since these sites are the main targets for toxicity. People with impaired esterase production would be unusually susceptible to ethion exposure because of a reduced ability to metabolize ethion absorbed by the body. This population would include people suffering from liver diseases (hepatitis, cirrhosis). Pregnant women have lower levels of plasma cholinesterase and are more susceptible to agents such as succinylcholine, which is metabolized by this enzyme. Ethion can bind stoichiometrically to this enzyme and inhibit its activity, so pregnant women are at least hypothetically more susceptible to ethion exposure than other populations. A similar effect could be expected in individuals with inherited abnormally low plasma cholinesterase levels. Individuals may not know if they have decreased plasma cholinesterase and other esterases and, therefore, may not know that they are more susceptible to the effects of ethion.

2.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to ethion. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to ethion. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to ethion:

"Cholinesterase inhibitor pesticides" in *Handbook of Poisoning*, 1987, Appleton and Lange, Norwalk, CT; R.H. Dreisbach and Robertson, WO

"Organophosphates and other insecticides" in *Clinical Management of Poisoning and Drug Overdose*, 2nd edition, 1990, W.B. Saunders, Philadelphia; L.M. Haddad and J.F. Winchester, eds.

"Insecticides: Organophosphates and carbamates" in *Goldfrank's Toxicologic Emergencies*, 5th ed., 1994, Norwalk; C.K. Aaron and M.A. Howland.

2.11.1 Reducing Peak Absorption Following Exposure

If exposure has occurred by the oral route, gastric lavage would reduce peak absorption if the treatment is given shortly after exposure. Treatment with activated charcoal would probably also be effective. If exposure has occurred by the dermal route, rinsing the exposed skin with large amounts of flowing water and soap would greatly reduce exposure.

2.11.2 Reducing Body Burden

Because ethion does not accumulate in the body and appears to be rapidly metabolized, specific efforts to reduce the body burden would not appear to be necessary.

2.11.3 Interfering with the Mechanism of Action for Toxic Effects

Ethion has the same mechanism of action as other organophosphorus insecticides. Poisonings with these types of chemicals are common enough that specific and effective medical interventions have been developed. The life-threatening effects of ethion poisoning are related to its effects on the respiratory system (respiratory depression, bronchospasm, increased bronchial secretions, pulmonary edema, muscular weakness). If these symptoms are present, artificial respiration and suctioning are performed via an endotracheal tube. Atropine is used to counteract the muscarinic effects of ethion, with care being taken that symptoms of atropine overdose do not occur (dry mouth, dilatation of the pupils).

Pralidoxime (2-PAM or Protopam), a cholinesterase reactivator, can be used as an antidote for organophosphate poisoning, and is typically given in conjunction with atropine. Enzyme reactivation, accomplished by hydrolysis of the oxygen-phosphorus bond, occurs most markedly at the neuromuscular junction, restoring skeletal muscle response and, importantly, normalizing diaphragm excursion and respiratory effort. Pralidoxime must be administered as rapidly after organophosphate exposure as possible, as its efficacy is inhibited by the “aging” phenomenon. The “aging” involves a chemical

change in the organophosphate-enzyme complex and occurs within minutes to hours (see Section 2.4.2 for more details). The resulting compound, a monoethoxyphosphorylated acetycholinesterase molecule, is very stable and resistant to the effects of pralidoxime.

2.12 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of ethion is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of ethion.

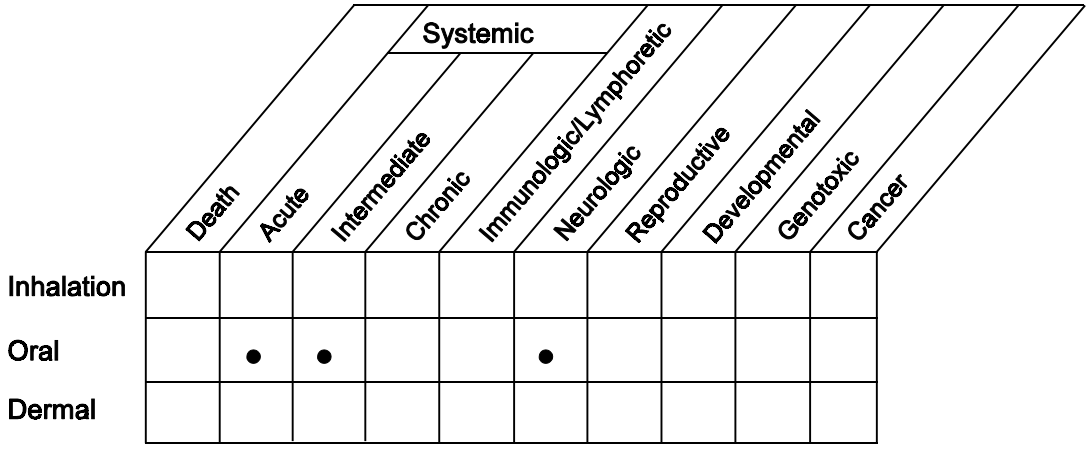
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.12.1 Existing Information on Health Effects of Ethion

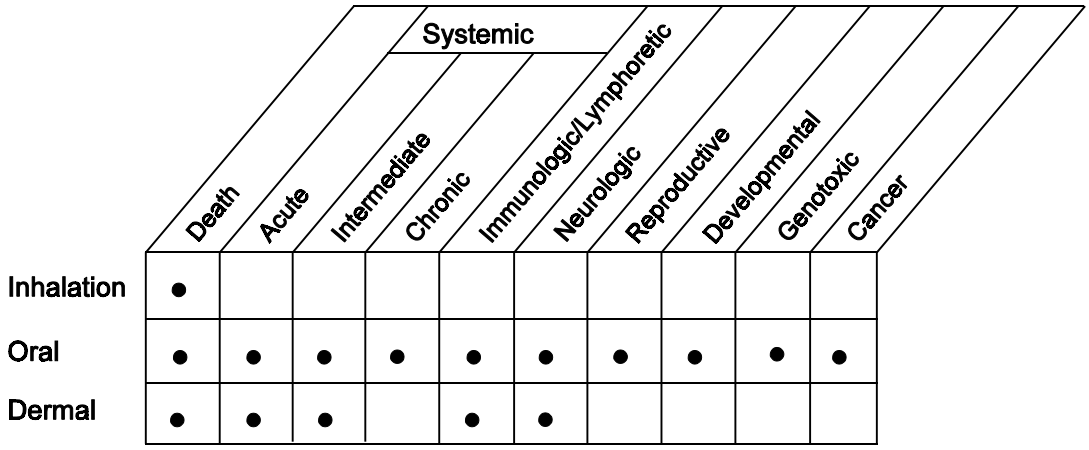
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of ethion. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As shown in Figure 2-4, information on health effects of ethion in humans is limited to systemic and neurological effects. A case report of a poisoning incident (Comstock et al. 1967) and an unpublished

Figure 2-4. Existing Information on Health Effects of Ethion



Human



Animal

● Existing Studies

intermediate-duration oral exposure study in volunteers (Palazzolo 1970) are available. No studies describing health effects in humans after inhalation or dermal exposure for any duration or chronic-duration oral exposure were located.

Information on health effects in animals after exposure to ethion is far more extensive (see Figure 2-4). However, almost all of these studies were performed to satisfy EPA pesticide registration requirements and have not been published in the open literature.

2.12.2 Identification of Data Needs

Acute-Duration Exposure. Populations in the vicinity of hazardous waste sites may be exposed to ethion for brief periods. Exposure would most likely occur by contact with contaminated soil, but drinking contaminated water is also possible. The central and peripheral nervous systems are the major target organs for ethion toxicity by the oral and dermal routes. The specific target of ethion is the enzyme that catalyzes the hydrolysis of the neurotransmitter acetylcholine, neural acetylcholinesterase. High doses of ethion can be extremely toxic by the oral route as demonstrated by a case report of a 6-month-old boy where a single oral dose of 15.7 mg/kg would have been fatal without aggressive medical intervention (Comstock et al. 1967). Threshold doses for clinical effects and/or cholinesterase/acetylcholinesterase inhibition after oral exposure to ethion are available for several species including humans, rats, mice, dogs and rabbits. Threshold doses for acetylcholinesterase inhibition after dermal exposure in the rabbit are also available (Weiner 1985a, 1985b cited in EPA 1989d).

The intermediate-duration oral MRL of 0.002 mg/kg/day derived for ethion based on a NOAEL of 0.06 mg/kg/day for inhibition of brain acetylcholinesterase in Beagle dogs (Bailey 1988) is applicable to acute-duration exposures as well. The acute-duration oral toxicity of ethion is well understood, and no further studies appear necessary. Inhalation exposure at hazardous waste sites to levels that produce detectable toxic effects is unlikely. Since the most likely route of exposure to ethion at hazardous waste sites is dermal contact with contaminated soil, a study that establishes a threshold value for acetylcholinesterase inhibition in a second species may be useful for risk assessment.

Intermediate-Duration Exposure. An intermediate-duration oral MRL of 0.002 mg/kg/day was derived for ethion based on a NOAEL of 0.06 mg/kg/day for inhibition of brain acetylcholinesterase in

dogs (Bailey 1988). A well conducted study in humans is available on the effects of intermediate-duration oral exposure to ethion (Palazzolo 1970). Results in animal studies indicate that the toxic effects of intermediate-duration exposure to ethion are similar to those for the acute-duration by both the oral and dermal routes. No further intermediate-duration studies in animals would appear to be necessary.

Chronic-Duration Exposure and Cancer. There is limited information regarding the potential toxic effects of chronic, low-level exposure to ethion. A chronic-duration oral MRL of 0.0004 mg/kg/day was derived for ethion based on a NOAEL of 0.06 mg/kg/day for inhibition of brain acetylcholinesterase in Beagle dogs in an intermediate-duration study (Bailey 1988). A chronic-duration (2-year) oral study has been done in rats and mice and produced no evidence of carcinogenicity by this route (Morrow 1985a, 1985b). No neurological or systemic effects were found at the doses (1.12–2 mg/kg/day) used in this study. Chronic-duration exposure is the most likely type of exposure that would be experienced by people living near hazardous waste sites containing ethion. This exposure is most likely to be by dermal contact with contaminated soil, although drinking contaminated water or soil ingestion by children could cause oral exposure. Exposure to ethion contaminated dust is not likely to cause intoxication.

Genotoxicity. Ethion has been tested for genotoxicity in several *in vitro* test systems and has tested uniformly negative both with and without metabolic activation. A single *in vivo* study in chickens showed an increase in sister chromatid exchanges following oral ethion exposure (Bhunya and Jena 1994). Further *in vivo* tests in rats or mice are needed to confirm these results.

Reproductive Toxicity. No information on reproductive toxicity in humans after ethion exposure is available. Ethion did not cause reproductive toxicity by the oral route in a 3-generation study in rats or histopathological evidence for damage to reproductive tissues in intermediate- or chronic-duration studies. Ethion is not known to be an endocrine disruptor. Further studies on reproduction in animals after exposure to ethion would not appear to be necessary.

Developmental Toxicity. No information on developmental toxicity in humans after ethion exposure is available. Ethion did not cause teratogenicity in rats or rabbits, although skeletal abnormalities were seen at maternally toxic doses. Additional animal studies in which neurobehavioral, immunological, and reproductive end points are assessed up through sexual maturity following pre- and postnatal exposure may be helpful to determine if developmental effects become apparent after birth.

Immunotoxicity. Ethion has tested negative in a skin sensitization study in guinea pigs. No reports of allergic contact dermatitis after exposure to ethion in humans were located. It appears that further immunotoxicity studies are not necessary.

Neurotoxicity. The neurotoxicity of ethion via acetylcholinesterase inhibition is understood. A no effect level is available for humans and threshold doses for acetylcholinesterase inhibition have been established for several species. A delayed neurotoxicity test was negative in chickens for ethion. Additional animal studies do not seem to be warranted at this time.

Epidemiological and Human Dosimetry Studies. Epidemiological/occupational studies would be useful for adequately assessing risk of exposure to ethion. At the present time, very few people are exposed to ethion outside occupational groups. The major group potentially exposed, pest control workers, generally use several different pesticides, and it may be difficult to identify a group exposed primarily to ethion. However, well designed epidemiological studies of exposed workers that examine the effects of ethion on the nervous system would be useful for establishing cause/effect relationships.

Biomarkers of Exposure and Effect.

Exposure. Reliable biomarkers for exposure to ethion already exist (plasma cholinesterase, erythrocyte acetylcholinesterase, and clinical symptoms of neurotoxicity). However, reliable methods to distinguish ethion intoxication from that caused by other organophosphorus compounds do not exist.

Effect. Reliable biomarkers for the effect of ethion exist (cholinergic symptoms of neurotoxicity and erythrocyte acetylcholinesterase).

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetics of ethion are not well understood. Two major data needs were identified. Studies should be done where ethion and ethion monoxon are measured in tissues rather than radioactivity derived from labeled ethion. The metabolites of ethion (besides diethyl phosphate) have not been identified beyond their solvent extraction behavior. Without this information, the potential toxicity of metabolites cannot be assessed.

Comparative Toxicokinetics. No data needs have been identified for comparative toxicokinetics.

Methods for Reducing Toxic Effects. Further studies on retarding gastrointestinal absorption of ethion and the effectiveness of absorbents would be useful in the treatment of poisoning. No methods exist for increasing the excretion of ethion and the active metabolite ethion monoxon. The medical management of the toxic effects of ethion (respiratory support, atropine treatment, reactivation of neural acetylcholinesterase with oximes) is similar to that for poisoning by other organophosphate insecticides. Any improvements in the management of organophosphate poisoning would apply to ethion.

Children's Susceptibility There are no populations of children identified that are specifically exposed to ethion. Poisonings of children by this chemical appear to be exceedingly rare since only one case report could be found in the literature (Comstock et al. 1967). The clinical course for this 6-month-old was very similar to that seen in adults poisoned by other organophosphate insecticides, and his recovery appeared to be complete as late as one year post-exposure. In future incidents of ethion poisoning of children and adults, better estimates should be made of exposure level, exposure route, and metabolite levels relative to the observed symptoms of toxicity. The only animal study comparing effects of ethion between juveniles and adults showed marginally greater toxicity (lower LD_{50}) in juvenile rats after intraperitoneal injection (Brodeur and DuBois 1963). Additional animal studies examining nonlethal end points in juvenile and adult animals following ethion exposure are needed. In particular, studies examining the dermal and oral routes of exposure would be the most useful.

It is conceivable that children, particularly very young children, may be more susceptible to the effects of ethion than adults, due to suspected differences in metabolic activities. However, comparative metabolic data for ethion in children and adults is lacking, specifically data regarding cytochrome P450 and esterase activities. Data are also lacking as to whether there are differences in absorption, distribution, or excretion of ethion between children and adults. Additional animal pharmacokinetic and metabolic studies comparing fetal, juvenile and adult animals, preferably supplemented with studies utilizing human tissues where appropriate, will be needed to clarify these issues. Biomarkers of exposure need to be further studied in order to better estimate human exposure at all age levels following acute or chronic exposure to ethion. Also, developmental studies in animals are needed to quantitatively measure placental transfer of ethion and its metabolites and to determine whether ethion and its metabolites can be metabolized by placental tissue.

Child health data needs relating to exposure are discussed in Section 5.8.1 Identification of Data Needs: Exposures of Children.

2.12.3 Ongoing Studies

No ongoing studies on ethion were located.