3. HEALTH EFFECTS

3.1 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 methyl parathion. 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.

3.2 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 (LOAELs) 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 methyl parathion. 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 1990c), 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.

3.2.1 Inhalation Exposure

3.2.1.1 Death

Deaths following exposure to methyl parathion occurred in children (two sisters, aged 4 and 11 years). Exposure was by multiple routes including inhalation of methyl parathion that was sprayed inside a house from a solution containing 4% methyl parathion (1.25% methyl parathion was recommended by a manufacturer for field spraying). Thirteen days after spraying, the house air contained 0.041 mg/m^3, 7 times the concentration of methyl parathion found just outside. Drinking water, stored in open containers due to the lack of running water in the house, contained 0.138–0.275 mg/L of methyl parathion 12 days after spraying. Dermal exposure may also have been possible. All children in the household, including five surviving siblings, had depressed plasma and erythrocyte cholinesterase levels. Urinary 4-nitrophenol was detected in three children. Clinical signs and symptoms were typical of organophosphate toxicity, as described in Section 3.2.1.4, with respiratory arrest as the terminal event (Dean et al. 1984).

Death from a combination of inhalation and dermal exposures has been reported by Fazekas (1971) in four individuals who used methyl parathion (Wofatox) spray in a careless manner. These individuals were part of a larger series of 30 cases (20 men, 10 women) of fatal methyl parathion intoxication reported by Fazekas (1971). Since 26 of these fatalities followed oral exposure, this report is discussed in detail in Sections 3.2.2.1 and 3.2.2.2.

The LC_{50} values of methyl parathion have been established in rats. A 1-hour LC_{50} of 200 mg/m^3 and a 4-hour LC_{50} of 120 mg/m^3 for males were determined by Kimmerle and Lorke (1968). One-hour LC_{50} values of 257 mg/m^3 for male rats and 287 mg/m^3 for female rats were determined for 70–80% pure methyl parathion by EPA (1978e); the rats were exposed to aerosols of respirable size. Survivors of toxic doses recovered clinically by 10–14 days postexposure. Sex-related differences in acute mortality of rodents have also been observed after exposure to methyl parathion by other routes (Murphy and Dubois 1958).

The LC_{50} value for male rats for the acute-duration category is recorded in Table 3-1 and plotted in Figure 3-1.

Table 3-1. Levels of Significant Exposure to Methyl Parathion - Inhalation

Key to[a] figure	(strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat	1-4 hr once				120 M (LC_{50})	Kimmerle and Lorke 1968

[a]The number corresponds to entries in Figure 3-1.

hr = hour(s); LC_{50} = Lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; mg/m^3 = milligram per cubic meter; NOAEL = no-observable-adverse-effect level

Figure 3-1. Levels of Significant Exposure to Methyl Parathion - Inhalation

Acute (≤14 day)

3.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, hematological, musculoskeletal, or dermal effects in humans or animals after inhalation exposure to methyl parathion. Dean et al. (1984) reported that seven children exposed to methyl parathion by many routes exhibited pinpoint pupils, abdominal pain, and diarrhea. The respiratory, cardiovascular, hepatic, and renal effects reported by Fazekas (1971) that were found in humans acutely exposed to methyl parathion intoxication resulted from exposure by all three routes; however, the results did not distinguish between the routes.

Respiratory Effects. Pulmonary edema was reported in humans dying from acute methyl parathion (Wofatox) intoxication (Fazekas 1971). Edema was found in a man who died 2 hours after intoxication, and, in other cases, edema was found in others who died as long as 9 days after exposure. Broncho-constriction and hypersecretion of bronchial glands (bronchorrhea) are primary muscarinic effects of methyl parathion. The broncoconstriction, bronchorrhea, and bradycardia caused by methyl parathion are strongly conducive to pulmonary edema.

Rats exposed to a 1-hour LC_{50} of methyl parathion (see Section 3.2.1.1) had moderate pulmonary congestion, hemorrhage, and edema (EPA 1978e). While these lesions could represent an irritant effect of inhaled aerosols of methyl parathion, they also may be secondary to agonal death, meaning resulting from the death process, or to muscarinic effects as noted in the previous paragraph.

Cardiovascular Effects. Lesions in the heart and blood vessels have been reported in humans acutely intoxicated with methyl parathion (Wofatox) (Fazekas 1971) and are discussed in Section 3.2.2.2. However, many of these lesions may be secondary to the effects of methyl parathion on the conduction system of the heart, to other components ingested, or to therapeutic regimens that some of these patients received.

Thymic hemorrhage and congested cerebral blood vessels occurred in rats exposed to a 1-hour LC_{50} of methyl parathion described in Section 3.2.1.1 (EPA 1978e). These are probably nonspecific agonal lesions.

Hepatic Effects. Liver lesions were reported in humans dying of acute methyl parathion (Wofatox) intoxication (Fazekas 1971). See Section 3.2.2.2 for a description of these lesions. The hepatic effects

were nonspecific and were likely a reflection of systemic effects of hypoxia, stress, therapeutic agents, or a combination of all of these.

No studies were located regarding hepatic effects in animals after inhalation exposure to methyl parathion.

Renal Effects. Kidney lesions were reported in humans dying of acute methyl parathion (Wofatox) intoxication (Fazekas 1971). See Section 3.2.2.2 for a description of these lesions.

No studies were located regarding renal effects in animals after inhalation exposure to methyl parathion.

Ocular Effects. One study reported that seven children exposed to methyl parathion by inhalation, oral, and possibly dermal routes exhibited pinpoint pupils (miosis) (Dean et al. 1984). This effect is a consequence of the effects on the autonomic nervous system. No other studies were located regarding ocular effects in humans or animals after inhalation exposure to methyl parathion.

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to methyl parathion.

3.2.1.4 Neurological Effects

Neurological effects related to cholinesterase depression occurred in seven children acutely exposed to methyl parathion by inhalation as well as orally and dermally (Dean et al. 1984). The children were admitted to a local hospital with signs and symptoms of lethargy, increased salivation, increased respiratory secretions, and miosis. Two of the children were in respiratory arrest. Two children died within several days of each other. All of the children had depressed plasma and erythrocyte cholinesterase levels (Table 3-2). These effects are similar to those occurring in methyl parathion intoxication by other routes (see Sections 3.2.2.4 and 3.2.3.4). Three adults exposed in the same incident had normal plasma (apart from one female) and red blood cell cholinesterase, and urinary levels of 4-nitrophenol (0.46–12.7 ppm) as high as some of the ill children.

Table 3-2. Plasma and Erythrocyte Cholinesterase Levels in Children Intoxicated by Methyl Parathion[a]

Age/sex	Plasma cholinesterase (mU per mL per minute)[b]	Erythrocyte cholinesterase (ΔpH/hour)[c]
11 years/female (died)	No data	No data
9 years/male	1,023	0.15
8 years/male	987	0.10
6 years/female	1,707	0.10
5 years/female	964	0.10
4 years/female (died)	914	0.00
2 years/female	1,534	0.10

[a]Adapted from Dean et al. 1984
[b]Normal value: 2,450–4,850
[c]Normal value: 0.57–0.98

Δ = change; mU = milliunits; mL = milliliter

Male rats exposed to 264 mg/m^3 of methyl parathion by inhalation had 59% (range: 53–61%) inhibition of blood (a combination of erythrocyte and plasma) cholinesterase 1 hour after exposure (EPA 1978e). These animals had typical cholinergic signs of toxicity: salivation, exophthalmos, lacrimation, spontaneous defecation and urination, and muscle fasciculation. Values for controls were not provided. Death was not correlated to the degree of cholinesterase inhibition in whole blood.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after inhalation exposure to methyl parathion.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to methyl parathion.

3.2.1.7 Cancer

No studies were located regarding carcinogenic effects in humans or animals after inhalation exposure to methyl parathion.

3.2.2 Oral Exposure

3.2.2.1 Death

There have been a number of cases of human intoxication and death from oral exposure to methyl parathion.

Two of seven children who ingested methyl parathion in contaminated drinking water, and also were exposed by inhalation and possibly by dermal contact following spraying of methyl parathion inside a house, died (Dean et al. 1984). Additional details are provided in Section 3.2.1.1.

A 50-year-old white male died after intentional methyl parathion ingestion (Wofatox liquid) (Fazekas and Rengei 1964). The estimated dose of methyl parathion was 1,840 mg. Gross necropsy findings consisted

of congested cerebral meninges, brain edema, generalized visceral congestion, laryngeal and pulmonary edema, fatty liver, intense congestion of the esophageal mucosa, and petechial hemorrhages on the mucosa of the stomach and intestines. Histopathologic examination of tissues was not performed. The estimated dose of 1,840 mg methyl parathion corresponds to a bolus dose of 26 mg/kg. None of the reported autopsy findings are specific to organophosphate intoxication. A lethal oral dose of 307–660 mg has been reported for adults (Fazekas and Rengei 1964).

Thirty fatalities, 20 men and 10 women, resulted from acute exposure to methyl parathion (Wofatox) (Fazekas 1971). Patients ranged in age from 18 to 82 years. They died between 2 hours and 9 days after exposure to Wofatox. A number of these individuals received intensive therapy but died nonetheless. Of the 30 cases, 26 had intentionally ingested 50–300 g of Wofatox, while the rest had a combination of excessive dermal and inhalation exposure during spraying. Histological lesions were reported in liver, kidney, spleen, heart, brain, and vascular endothelium. Lesions were not categorized by exposure route. These lesions are described in Section 3.2.2.2 under the various organ systems and in Section 3.2.2.4 under neurological effects. Most of these lesions are not specific for methyl parathion in particular or organophosphates in general.

Numerous studies in experimental animals have established LD_{50} values for acute oral exposure to methyl parathion. In most of these studies, technical grade, purified methyl parathion, or an emulsion concentration (EC) formulation was administered by gavage in a vehicle such as propylene glycol. Species tested were rats (EPA 1978e; Gaines 1960; Miyamoto et al. 1963b; Sonnenschein et al. 1989b; Yamamoto et al. 1982), mice (El-Herrawie and El-Sayed 1986; Haley et al. 1975b; Metcalf and March 1953; Miyamoto et al. 1963b), and guinea pigs (Miyamoto et al. 1963b).

In rats, the LD_{50} for males tended to be lower, although not statistically significantly different, in comparison with that for females (EPA 1978e; Gaines 1960). In CD-1 mice, males had a significantly lower LD_{50} than did females (Haley et al. 1975b). Similar sex-related differences have been seen with some other thio-organophosphate pesticides and were attributed to more efficient conversion of these compounds to their active paraoxon metabolites in the liver of males (Murphy and DuBois 1958).

The LD_{50} values for methyl parathion were compared to those for methyl paraoxon, the active metabolite of methyl parathion, in rats, guinea pigs, and mice by Miyamoto et al. (1963b). Methyl paraoxon was 5.4 times more potent than methyl parathion in male rats, 5 times more potent in male guinea pigs, and 1.6 times more potent in mice.

In mice, heat-induced isomers of purified methyl parathion were less lethal than was purified methyl parathion alone (LD_{50} of >200 mg/kg for heat-induced isomers compared to 100–200 mg/kg for methyl parathion) (Metcalf and March 1953). Eighty-five percent of the sample was heat-isomerized, but the isomers were not precisely identified. Methyl parathion in an emulsifiable concentrate had greater acute (24 hours) oral lethality for male mice than it did in the technical or microencapsulated formulations. For microencapsulated methyl parathion, the toxicity of the supernatant increased over storage time from an LD_{50} value of 21.2 mg/kg before storage to 14.9 mg/kg at 2 months storage time, indicative of gradual release of methyl parathion from the capsules to the liquid during storage (El-Herrawie and El-Sayed 1986).

Clinical signs of acute oral toxicity of methyl parathion and methyl paraoxon were characterized by Miyamoto et al. (1963b) in rodents. Signs occurred within minutes after compound administration and consisted of dyspnea, twitching, clonic convulsions, salivation, chromodacryorrhea, and exophthalmos. The signs lasted for 30–60 minutes, at which time death usually occurred. However, guinea pigs tended to develop less severe signs, and deaths occurred up to 24 hours postdosing.

An 8-week dietary study of methyl parathion was performed by NCI (1979) in order to select doses for a chronic bioassay. F344 rats of both sexes (five animals/sex/group) received doses of 0, 0.5, 1, 1.5, 2, or 2.5 mg/kg/day. $B6C3F_1$ mice (five animals/sex/group) received doses of 0, 2.6, 5.2, 7.8, 10.4, 13, 16.2, 32.5, or 65 mg/kg/day. All male rats survived to study termination. One of five females fed 0.5, 1.5, and 2 mg/kg/day and two of five females fed 2.5 mg/kg/day died. In mice, significant mortality occurred at the two highest doses; all males died in the 32.5- and 65-mg/kg/day groups, as did all females in the 65-mg/kg/day group. Clinical signs in both sexes in the 32.5- and 65-mg/kg/day dosage groups were rough hair coat and arched back. The results suggest that male mice may be more susceptible than females to intermediate-duration exposure, in contrast to the acute lethality data for mice and to the results for rats in this intermediate-duration study.

All reliable lethal doses (LD_{50} values) for each species and for the acute- and intermediate-duration categories are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

Reductions in erythrocyte and plasma cholinesterase levels are considered biomarkers of neurological effects and not hematological effects as discussed in Sections 3.2.2.4 and 3.5.2.

Table 3-3. Levels of Significant Exposure to Methyl Parathion - 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 Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat	once (G)				12[b] M (LD_{50}) 18 F (LD_{50})	EPA 1978e
2	Rat	once (G)				14[b] M (LD_{50}) 24 F (LD_{50})	Gaines 1960
3	Rat	once (G)				24.5 M (LD_{50})	Miyamoto et al. 1963b
4	Rat	10 d 1x/d (G)				4 M (6/6 died)	Yamamoto et al. 1982
5	Mouse	once (G)				10.3 M (LD_{50} for EC formulation)	El-Herrawie and El-Sayed 1986
6	Mouse	once (G)				12.4 M (LD_{50} for technical formulation)	El-Herrawie and El-Sayed 1986
7	Mouse	once (G)				14.5[b] M (LD_{50}) 19.5 F (LD_{50})	Haley et al. 1975b
8	Mouse	once (NS)				100 (LD_{50})	Metcalf and March 1953
9	Mouse	once (G)				17 (LD_{50})	Miyamoto et al. 1963b

Table 3-3. Levels of Significant Exposure to Methyl Parathion - 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 Chemical Form
10	Gn Pig	once (G)				417 M (LD_{50})	Miyamoto et al. 1963b
	Systemic						
11	Rat	once (GW)	Cardio			9.5 (cardiac abnormalities)	Galal et al. 1975
12	Rat	once (GO)	Hepatic		15.6 (hepatocellular damage)		Sonnenschein et al. 1989a, 1989b
	Neurological						
13	Rat	14 d 1x/d Gd6-19 (GO)				1.5 F (muscle fasciculations, tremors in dams)	Gupta et al. 1985
14	Rat (Wistar)	10 d 1 x/d Gd 6-15 (GO)		1.0 F		1.5 F (muscle fasciculations, tremors, convulsions in dams)	Kumar and Devi 1996
15	Rat	10 d 1x/d (GO)			1.3 M (44% decreased plasma and 25% decreased brain cholinesterase levels)		Yamamoto et al. 1982
16	Rat	once (GO)				5 M (convulsions)	Youssef et al. 1987

Table 3-3. Levels of Significant Exposure to Methyl Parathion - 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 Chemical Form
Developmental							
17	Rat	9 d 1x/d Gd 7-15 (GO)				1 (impaired behavior; pup mortality)	Crowder et al. 1980
18	Rat (Wistar)	Gd 5-15 1x/d (G)		0.88 M			Desi et al. 1998
19	Rat	10-14 d 1x/d Gd6-15/19 (GO)			1 (decreased protein synthesis)		Gupta et al. 1984
20	Rat	14 d 1x/d Gd6-19 (GO)				1.5 (resorptions)	Gupta et al. 1985
21	Rat (Wistar)	10 d 1 x/d Gd 6-15 (GO)		1.0		1.5 (resorptions)	Kumar and Devi 1996

Table 3-3. Levels of Significant Exposure to Methyl Parathion - 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 Chemical Form
	INTERMEDIATE EXPOSURE						
	Death						
22	Rat	8 wk ad lib (F)				2.5 F (2/5 died)	NCI 1979
23	Mouse	8 wk ad lib (F)				32.5 M (5/5 died)	NCI 1979
	Systemic						
24	Rat (Wistar)	28 d 1x/d (GW)	Hemato	0.218 M	0.436 M (5% decrease in mean corpuscular volume)		Undeger et al. 2000
			Bd Wt	0.872 M			
25	Mouse (B6C3F1)	28 d 1 x/d (GO)	Hemato	6 F			Crittenden et al. 1998
26	Mouse	8 wk ad lib (F)	Gastro			32.5 (gastric hemorrhage)	NCI 1979
27	Mouse Kunming	15 d 1 x/d (GO)	Bd Wt	5.0			Tian et al. 1997

Table 3-3. Levels of Significant Exposure to Methyl Parathion - 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 Chemical Form
28	Dog (Beagle)	13 wk (F)	Dermal	3.0 M			Daly 1989
			Ocular	3.0 M			
			Bd Wt	0.3 M	3.0 M (emaciation, dehydration in 2 of 8 dogs; 30% reduced body weight gain)		
Immunological/Lymphoreticular							
29	Rat	35 d 1x/d (G)			1.25 (97% decreased agglutinin titer)		Shtenberg and Dzhunusova 1968
30	Rat (Wistar)	28 d 1x/d (GW)		0.872 M			Undeger et al. 2000
31	Mouse Kunming	15 d 1 x/d (GO)		0.5	2.5 (36% increased T suppressor cell ratio)		Tian et al. 1997
Neurological							
32	Rat (Wistar)	13 wk Gd 5-15 Ld 2-28 Pd 28-84 1 x/d (GW)			0.22[c] M (electrophysiological effects in CNS and PNS)		Desi et al. 1998
33	Mouse (B6C3F1)	28 d 1 x/d (GO)		1 F	3 F (18% decreased brain AChE activity)		Crittenden et al. 1998

Table 3-3. Levels of Significant Exposure to Methyl Parathion - 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 Chemical Form
34	Dog (Beagle)	13 wk (F)		0.30	3.0 (decreased plasma 53-59%, erythrocyte 20-23%, and brain 43-54% cholinesterase activity)		Daly 1989
	Developmental						
35	Rat (Wistar)	Gd 5-15 Ld 2-28 1x/d (G)		0.88 M			Desi et al. 1998
36	Rat (Wistar)	15 d 1x/d Gd 6-20 (IN)				1.0 (slightly impaired behavior)	Gupta et al. 1985

Table 3-3. Levels of Significant Exposure to Methyl Parathion - 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 Chemical Form
CHRONIC EXPOSURE							
Systemic							
37	Rat	105 wk ad lib (F)	Resp	2			NCI 1979
			Cardio	2			
			Gastro	2			
			Hemato	2			
			Musc/skel	2			
			Hepatic	2			
			Renal	2			
			Dermal	2			
			Ocular	2			
			Bd Wt	2			

Table 3-3. Levels of Significant Exposure to Methyl Parathion - 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 Chemical Form
38	Rat (Sprague-Dawley)	26 mo (males) 28 mo (females)	Cardio	0.25 F	2.5 F (increased heart to body weight ratio)		Suba 1984
		(F)	Hemato	0.025[d] M	0.25[b] M (decrease in mean hematocrit, and erythrocyte counts)		
				0.25 F	2.5 F (decreases in mean hemoglobin)		
			Dermal	0.25	2.5 (alopecia)		
			Ocular	0.25	2.5 (retinal degeneration and bilateral atrophy; sub capsular cataracts)		
			Bd Wt	0.25	2.5 (6% reduced body weight)		
			Other	0.25	2.5 (increased food consumption; ano-genital staining)		
39	Mouse (B6C3F1)	102 wk ad lib	Resp	16.2			NCI 1979
		(F)	Cardio	16.2			
			Gastro	16.2			
			Musc/skel	16.2			
			Hepatic	16.2			
			Renal	16.2			
			Dermal	16.2			
			Ocular	16.2			
			Bd Wt	16.2			

Table 3-3. Levels of Significant Exposure to Methyl Parathion - 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 Chemical Form
40	Dog	1 yr (F)	Resp	0.3			Suba 1981
			Cardio	0.3			
			Gastro	0.3			
			Hemato	0.3			
			Musc/skel	0.3			
			Hepatic	0.3			
			Renal	0.3			
			Dermal	0.3			
			Ocular	0.3			
	Immunological/Lymphoreticular						
41	Dog	1 yr (F)		0.3			Suba 1981
	Neurological						
42	Rat (Sprague-Dawley)	26 mo (males) 28 mo (females) (F)		0.25 M	2.5 M (decreased plasma 67-88%, erythrocyte 9-20%, and brain 76-79% cholinesterase activity)	2.5 M (slight tremor, peripheral neuropathy)	Suba 1984

Table 3-3. Levels of Significant Exposure to Methyl Parathion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
	Reproductive						
43	Dog	1 yr (F)		0.3			Suba 1981

[a]The number corresponds to entries in Figure 3-2.
[b]Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[c]Used to derive an intermediate oral MRL of 0.0007 mg/kg/day; dose divided by an uncertainty factor of 300 (10 for extrapolation from animals to humans, 10 for human variability, and 3 for a minimal LOAEL).
[d]Used to derive a chronic oral MRL of 0.0003 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; d = day(s); F = female; (F) = feed; (G) = gavage; gastro = gastrointestinal;Gd = gestation day; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; (IN) = ingestion; Ld = lactation day; LD_{50} = Lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; mg/kg/day = milligram per kilogram per day; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; Pd = postnatal day; Resp = respiratory; wk = week(s); x = time; yr = year(s)

Figure 3-2. Levels of Significant Exposure to Methyl Parathion - Oral

Acute (≤14 days)

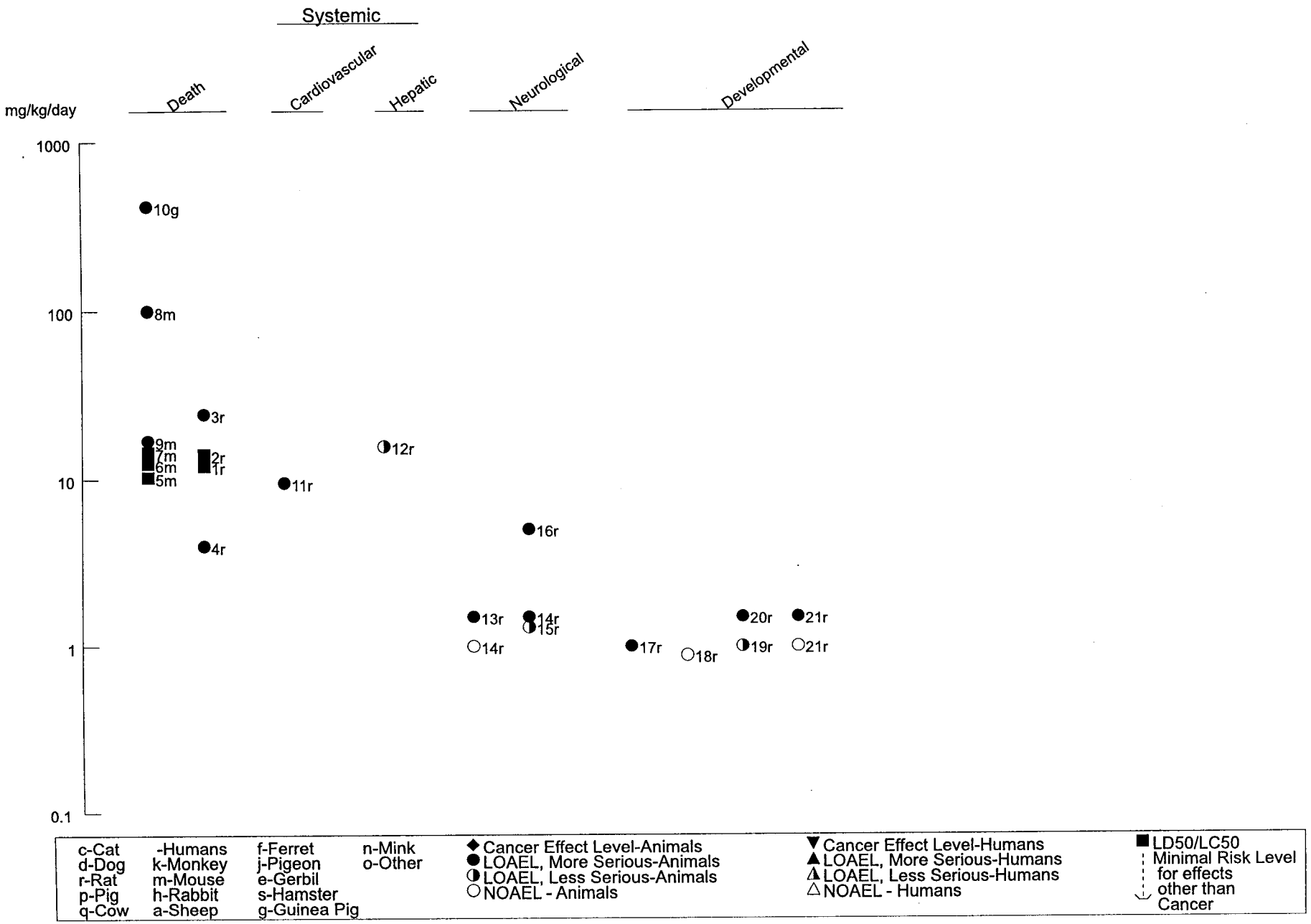


Figure 3-2. Levels of Significant Exposure to Methyl Parathion - Oral (*continued*)

Intermediate (15-364 days)

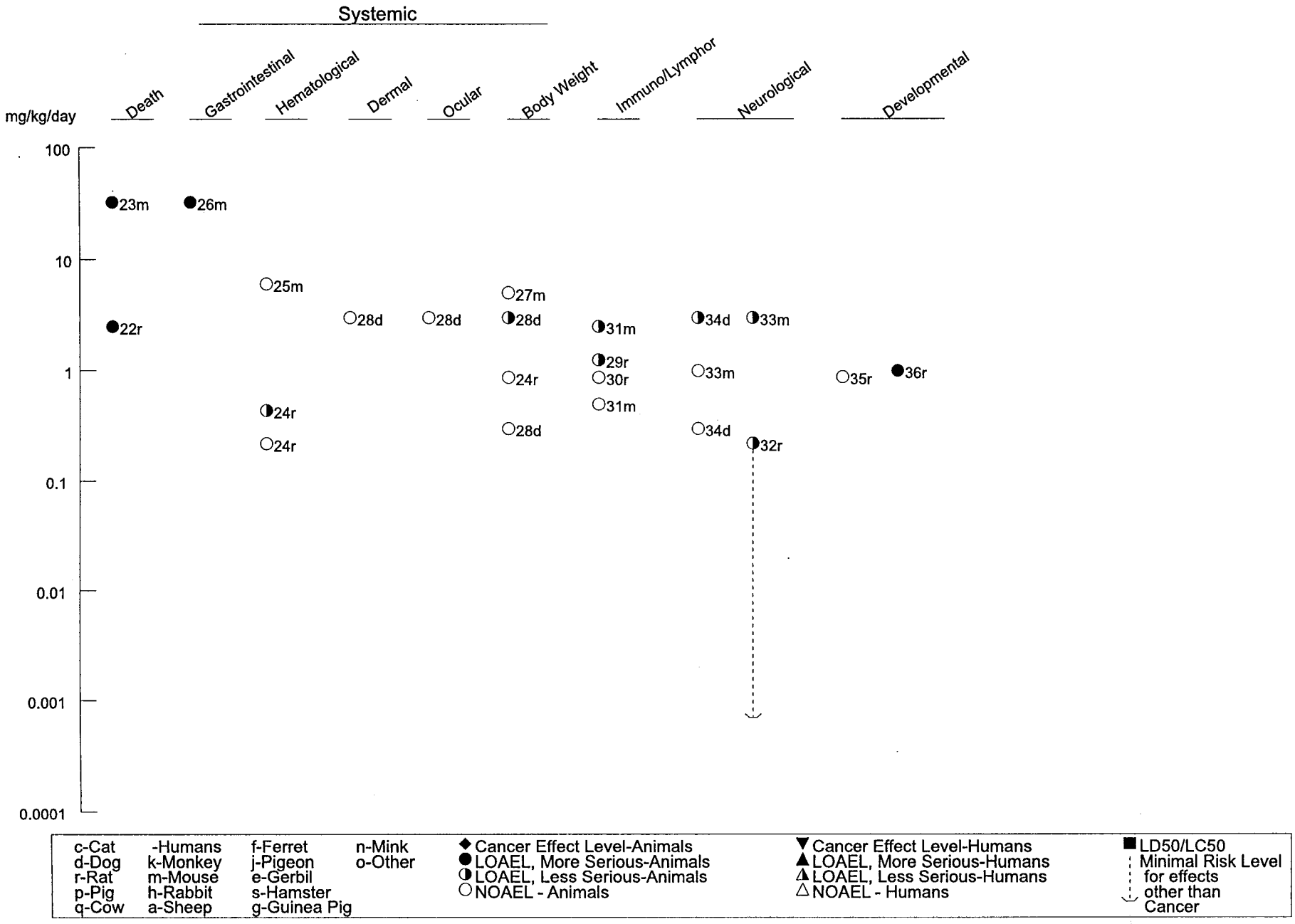
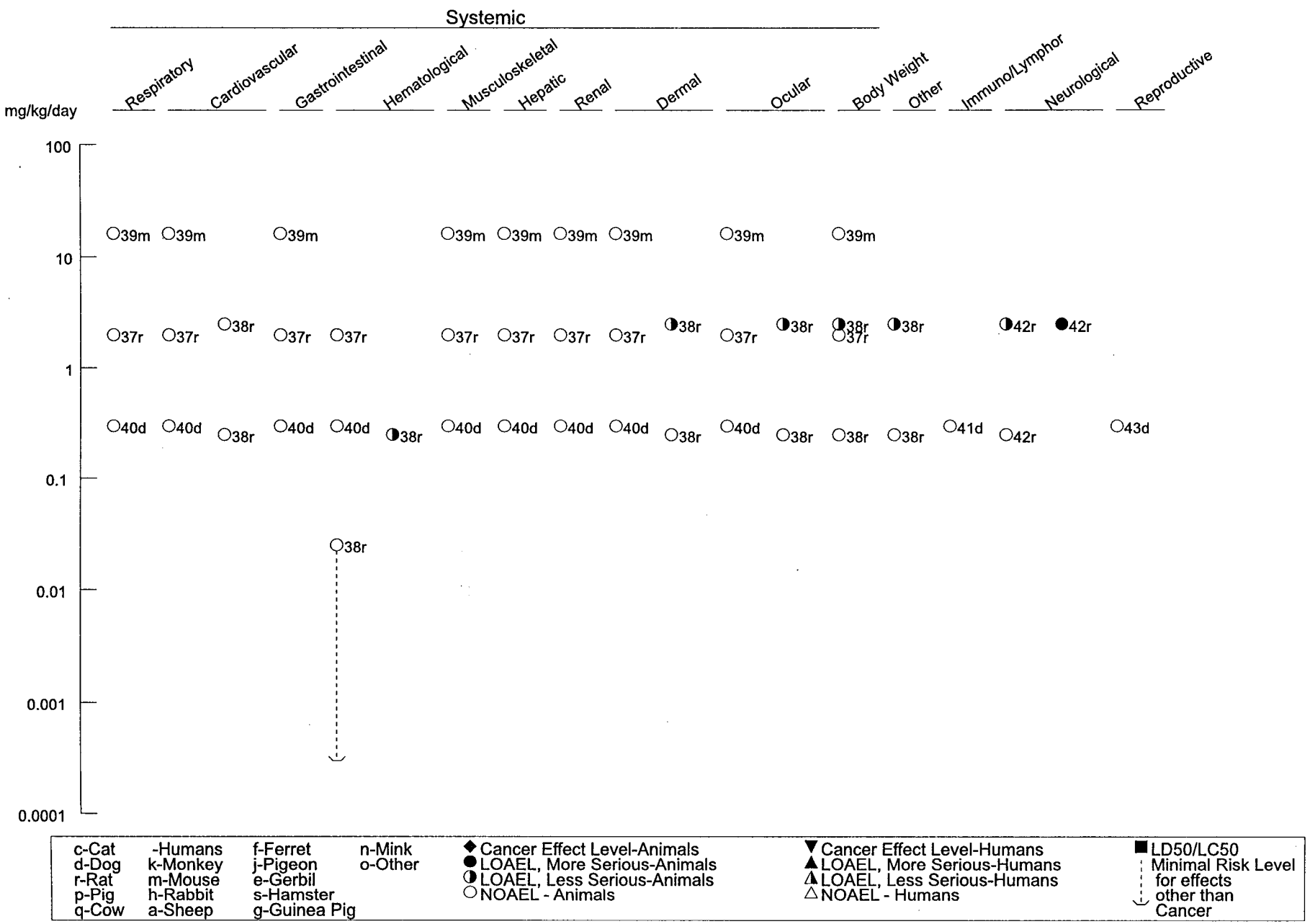


Figure 3-2. Levels of Significant Exposure to Methyl Parathion - Oral (*continued*)

Chronic (≥365 days)



The highest NOAEL and the reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-2.

Respiratory Effects. Pulmonary edema has been reported in humans who died of acute methyl parathion (Wofatox) intoxication (Fazekas 1971). Edema was found in a man who died 2 hours after intoxication and in others who died as long as 9 days after exposure. Bronchoconstriction and hyper-secretion of bronchial glands are primary muscarinic effects of methyl parathion. Pulmonary edema is not considered to be a primary effect of methyl parathion; it is considered to be secondary to the neurologic effects of this compound on the heart and vascular smooth muscle.

Routine gross and histopathological examinations revealed no treatment-related effects on the respiratory system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). Chronic dietary exposure to methyl parathion did not induce respiratory effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Cardiovascular Effects. Cardiovascular lesions were reported in some of the 30 cases of acute fatal intoxication by methyl parathion studied by Fazekas (1971). Patients who survived at least 20–24 hours had degeneration of the heart muscle with segmentation, fragmentation, and splitting of myofibers. Vascular lesions were congestion and multifocal hemorrhages in the central nervous system and in visceral organs. Patients surviving 28 hours to 9 days after intoxication (and receiving intensive therapy) had widespread swelling of vascular endothelium with areas of desquamation into vessel lumens. Blood vessel walls and perivascular spaces were edematous. However, many of these lesions may be secondary to the effects of methyl parathion on the conduction system of the heart, to other components ingested, or to therapeutic regimens that some of these patients received.

Rats exposed by gavage to 19 mg/kg (LD_{50} dose) or 9.5 mg/kg (half of the LD_{50} dose) of methyl parathion developed abnormalities in their heart rate and electrocardiograms (Galal et al. 1975). Bradycardia was observed in both groups 1 and 2 hours after oral introduction of the methyl parathion (85% reduction in rate in the LD_{50} group and 68% reduction in the one-half-LD_{50} group). Severe arrhythmia and electro-cardiographic abnormalities suggestive of myocardial ischemia also occurred. In comparison to malathion and carbaryl, methyl parathion produced the greatest cardiotoxic changes.

A significant increase in heart-to-body-weight ratio occurred in female rats exposed to 2.5 mg/kg/day methyl parathion in the diet for 2 years, but not in rats exposed to either 0.025 or 0.25 mg/kg/day methyl

parathion (Suba 1984). This effect did not have any complementary histopathology. Routine gross and histopathological examinations revealed no treatment-related effects on the cardiovascular system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). Chronic dietary exposure to methyl parathion did not induce cardiovascular effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Gastrointestinal Effects. Intense congestion of the esophageal mucosa and petechial hemorrhages in the stomach and intestine were reported in a patient who committed suicide by ingesting methyl parathion (Wofatox) (Fazekas and Rengei 1964). In a series of 30 cases of methyl parathion (Wofatox) fatalities, inflammation was present in the stomach and intestine at autopsy (Fazekas 1971). These victims died within 2 hours to 9 days after exposure, even after intensive therapy. All these gastro-intestinal findings are nonspecific and cannot be attributed to a primary effect of methyl parathion.

In an 8-week study to establish doses for a chronic dietary bioassay of methyl parathion, B6C3F_1 mice received dietary methyl parathion at levels of 0, 2.6, 5.2, 7.8, 10.4, 13, 16.3, 32.5, and 65 mg/kg/day. Gastric hemorrhage was present at necropsy in five of five males receiving 32.5 mg/kg/day and in three of five males and five of five females receiving 65 mg/kg/day (NCI 1979). This finding was correlated with mortality (see Section 3.2.2.1). Routine gross and histopathological examinations revealed no treatment-related effects on the gastrointestinal system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). Chronic dietary exposure to methyl parathion did not induce gastrointestinal effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to methyl parathion.

Total leukocyte and differential cell counts were not affected in female mice given 6 mg/kg/day of methyl parathion by gavage for 28 days (Crittenden et al. 1998). In male rats administered methyl parathion by gavage at doses of 0.218, 0.436, or 0.872 mg/kg/day for 28 days, the two highest dose groups exhibited dose-related significant decreases in mean corpuscular volume. No significant dose-related changes were seen in red blood cell count or absolute and differential white blood cell counts (Undeger et al. 2000). An additional intermediate-duration study in rats reported anemia (decreased hematocrit and erythrocyte count) and slight leukocytosis with neutropenia and lymphocytosis following treatment with an undetermined dose of methyl parathion, but higher than 0.37 mg/kg/day (Galal et al. 1977); this study is not presented in Table 3-2. Mean hemoglobin, hematocrit, and erythrocyte counts were significantly

reduced in female rats at 6–24 months of exposure to 2.5 mg/kg/day methyl parathion, which was given in the diet for 2 years (Suba 1984). Mean hematocrit and erythrocyte counts were significantly reduced in males at 24 months of exposure to either 0.25 or 2.5 mg/kg/day methyl parathion. These effects did not occur in rats exposed to 0.025 mg/kg/day methyl parathion. A NOAEL of 0.025 mg/kg/day was identified from these data. Based on this value, a chronic oral MRL of .0003 mg/kg/day was calculated as described in the footnote in Table 3-3. No treatment-related effects were noted following routine hematological testing in dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to methyl parathion.

Routine gross and histopathological examinations revealed no treatment-related effects on the musculoskeletal system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). Chronic dietary exposure to methyl parathion did not induce musculoskeletal effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Hepatic Effects. Liver lesions have been reported in humans acutely intoxicated by methyl parathion formulation (Wolfatox) (Fazekas 1971; Fazekas and Rengei 1964). These studies are discussed in detail in Section 3.2.2.1. Liver lesions were hepatocellular swelling, degeneration, and fatty change. Intoxicated patients surviving for 28 hours to 9 days had hepatocytes free in central or hepatic veins; this finding was described as mobilization of liver cells. The role of methyl parathion in the induction of all of these lesions is unclear.

Rats were given one or two LD_{50} doses of methyl parathion, spaced 14 days apart (Sonnenschein et al. 1989b). Male rats had elevated serum alanine aminotransferase indicative of hepatocellular damage. The enzyme levels returned to normal within 48 hours after exposure. Serum levels of tyrosine aminotransferase, an enzyme induced in liver by glucocorticoids, also increased. Liver lesions were more severe after the second dose of methyl parathion. They consisted of single cell necrosis of hepatocytes, hepatocellular swelling, binucleate hepatocytes, rare fatty vacuolization of hepatocytes, and Kupffer cell proliferation (Sonnenschein et al. 1989a). These changes may be secondary, stress-related findings rather than direct toxic effects of methyl parathion.

Routine gross and histopathological examinations revealed no treatment-related effects on the hepatic system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). Chronic dietary exposure to methyl parathion did not induce hepatic effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Renal Effects. Acute nephrosis has been reported in humans after acute, lethal intoxication (Fazekas 1971) by methyl parathion (Wofatox). This may be a secondary effect of hypoxia related to the neurologic effects of methyl parathion on vascular smooth muscle and on the electrical conduction system of the heart. It could also be related to therapeutic efforts.

Routine gross and histopathological examinations revealed no treatment-related effects on the renal system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). Chronic dietary exposure to methyl parathion did not induce renal effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

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

Routine gross and histopathological examinations revealed no treatment-related dermal effects on dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981).

There was an increased incidence of alopecia in female rats treated for 2 years with 2.5 mg/kg/day methyl parathion compared to either vehicle controls, high-dose males, or rats treated with either 0.025 or 0.25 mg/kg/day methyl parathion (Suba 1984). Chronic dietary exposure to methyl parathion did not induce dermal effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Ocular Effects. One study reported that seven children exposed to methyl parathion by inhalation, oral, and possibly dermal routes exhibited pinpoint pupils (miosis) (Dean et al. 1984). This effect is a consequence of the effects on the parasympathetic nervous system. No other studies were located regarding ocular effects in humans after oral exposure to methyl parathion.

There were no treatment-related effects on retinal function and no morphological effects on the eyes of dogs that were exposed to 0.03, 0.30, or 3.00 mg/kg/day methyl parathion for 13 weeks and allowed 4 weeks of no exposure to recover (Daly 1989).

Routine gross and histopathological examinations revealed no treatment-related effects on the ocular systems of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981).

Female rats exposed to 2.5 mg/kg/day methyl parathion exhibited retinal degeneration, which was noted at 24 and 28 months but not at 3 or 12 months of a 2-year treatment (Suba 1984). Posterior subcapsular cataracts also occurred in the high-dose females and may be related to retinal degeneration. These data are limited because the incidence of the effects was not reported with respect to controls or other treated groups and the statistical significance was not determined. The incidence of bilateral retinal atrophy was significantly greater in female rats that were chronically exposed to 2.5 mg/kg/day methyl parathion than in vehicle controls (Suba 1984). This effect was not significant in rats exposed to either 0.025 or 0.25 mg/kg/day methyl parathion. Chronic dietary exposure to methyl parathion did not induce ocular effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Body Weight Effects. No effect on body weight was seen in mice administered 5 mg/kg/day of methyl parathion by gavage for 15 days (Tian et al. 1997). Body weight gain in male rats was not affected by oral (gavage) administration of methyl parathion at 0.872 mg/kg/day for 28 days (Undeger et al. 2000). No effect on body weight gain was seen in male rats whose dams were administered 0.88 mg/kg/day during days 5–15 of gestation and from day 2 after delivery through weaning of the pups, which were then continued on the same doses for 8 weeks (Desi et al. 1998). Emaciation and dehydration were noted in two of eight male dogs treated with 3.00 mg/kg/day methyl parathion for 13 weeks in the diet, but not in dogs treated with either 0.03 or 0.30 m7g/kg/day methyl parathion (Daly 1989). These effects were reported to be due to treatment with methyl parathion, although the statistical significance of the effects was not determined. Also, male dogs treated with 3.00 mg/kg/day methyl parathion had a 30% decrease in body weight gain compared to controls. The other treatment groups did not exhibit this effect. There were no significant effects on mean body weights in any of the treatment groups.

Male and female rats exposed to 2.5 mg/kg/day methyl parathion in the diet for 2 years had statistically significant reduced body weights when compared to vehicle controls (Suba 1984). This effect was not consistent throughout the study and did not occur in rats exposed to either 0.025 or 0.25 mg/kg/day methyl parathion. Mean food consumption values were significantly elevated in male rats but only within the first 13 weeks of the 2-year exposure to 2.5 mg/kg/day methyl parathion (Suba 1984). Females exposed to 2.5 mg/kg/day methyl parathion had significantly reduced food intake values during the first 2 weeks of exposure, but intake was significantly elevated from week 3 to termination. Effects on food

consumption did not occur in rats exposed to 0.025 or 0.25 mg/kg/day methyl parathion. There were no treatment-related effects on body weight or food intake in dogs that were exposed to either 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). Also, no such effects were noted following chronic dietary exposure to methyl parathion in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Other Systemic Effects. Female rats, but not males, treated with 2.5 mg/kg/day methyl parathion had greater frequency of yellow ano-genital staining than the control females or females treated with either 0.025 or 0.25 mg/kg/day methyl parathion (Suba 1984).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to methyl parathion.

An increased ratio of T suppressor cells to T helper cells was seen in mice given 2.5 and 5.0 mg/kg/day of methyl parathion for 15 days; the spleen to body weight ratio was increased at 5 mg/kg/day (Tian et al. 1997). No other immunological or lymphoreticular end points were measured.

In female mice administered methyl parathion by gavage at doses of 1, 3, or 6 mg/kg/day for 28 days or 6 mg/kg/day for 7, 14, 21, or 28 days, natural killer cell activity was increased at 1 and 3 mg/kg/day (but not at 6 mg/kg/day at any duration) (Crittenden et al. 1998). Peritoneal macrophage activity was increased at all three doses, and cytotoxic T lymphocyte activity was not affected. Spleen cellularity (but not spleen weight) was increased at 7–21 days, but decreased at 28 days in mice receiving 6 mg/kg/day. The number of splenic plaque-forming cells following *in vitro* challenge with sheep red blood cells was decreased at all three doses of methyl parathion, in a dose-related manner. No decrease in antibody production was seen, however, when the mice were immunized with sheep red blood cells *in vivo* during methyl parathion treatment. Resistance to melanoma cells and to group b streptococci was not affected by methyl parathion. The results, taken together, do not indicate a serious decrement in immune function at these doses, which produced no overt cholinergic signs.

There was a suggestion of dose-related immunosuppressive effects in rabbits fed methyl parathion in the diet at 0.04, 0.16, 0.57, and 1.48 mg/kg/day for 4 weeks. These effects consisted of decreased numbers of plasma cells in popliteal lymph nodes (at all doses compared to controls), decreased numbers of germinal

centers in splenic white pulp, and atrophy of thymic cortical tissue (only at 0.57 mg/kg/day) (Street and Sharma 1975). Humoral immunity to NIISI typhoid vaccine was inhibited in rats given 1.25 mg/kg/day methyl parathion. This effect was noted when vaccination occurred prior to or during the 35–50-day period of exposure to methyl parathion (Shtenberg and Dzhunusova 1968).

The effects on the immune system may be related to stress (glucocorticoid) rather than a direct effect of methyl parathion, although a stress-related effect is more likely for neurotoxic doses (Kunimatsu et al. 1996).

No significant changes in immune function parameters (IgM-plaque forming cells assay, delayed-type hypersensitivity reaction) were observed in rats administered methyl parathion by gavage at doses of 0.218, 0.436, or 0.872 mg/kg/day for 28 days (Undeger et al. 2000). Routine gross and histopathological examinations revealed no treatment-related effects on the immune system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981).

The reliable LOAEL values for immunological effects in rats for the intermediate-duration category and the highest NOAEL in dogs for the chronic-duration category are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

Neurological effects related to cholinesterase depression occurred in seven children acutely exposed to methyl parathion by inhalation as well as orally and dermally (Dean et al. 1984). See Section 3.2.1.4 for additional details.

Neurologic signs and symptoms developed in 26 humans after intentional lethal intoxication by methyl parathion (Wofatox) via the oral route (Fazekas 1971). A number of the patients studied had considerable reduction (values not specified) in plasma cholinesterase activity. Typical signs and symptoms of intoxication by methyl parathion or other organophosphates are described in Section 3.5. Reductions in erythrocyte or plasma cholinesterase levels did not occur after two male university faculty volunteers ingested 2 mg/day of methyl parathion for 5 days and again 1–8 weeks later ingested 4 mg/day for 5 days (Rodnitzky et al. 1978). Neurobehavioral changes, as measured by a battery of tests, also did not occur. The subjects' predosing test values were the only controls for this study.

Neurologic signs did not occur over a 30-day period in male prisoner volunteers in California who ingested daily doses of methyl parathion ranging from 1.0 to 19 mg. There were no uniform changes in plasma or erythrocyte cholinesterase levels at any of these doses (Rider et al. 1969). By increasing concentrations of methyl parathion administered to the same experimental population and using the same protocol, a dose that inhibited cholinesterase values was established. These additional studies were published nearly 20 years ago in abstract form only; therefore, they are not discussed in this section.

Neurologic signs occurred in animals following oral exposure to methyl parathion at doses that caused reductions in erythrocyte, brain, and/or plasma cholinesterase levels. Male rats receiving 5 mg/kg orally by gavage developed cholinergic signs 7 minutes after dosing, with convulsions beginning within 16 minutes. Plasma cholinesterase was reduced to 43.6% of control levels (Youssef et al. 1987). Rats given methyl parathion by gavage at doses of 4 or 8 mg/kg/day developed cholinergic signs, and all rats died within 4 days. A single oral dose of 13 mg/kg or repeated doses of 1.3 mg/kg/day for 10 days induced significant inhibition of plasma and brain cholinesterase levels, with brain levels being 43% of the control value after the single dose and 56% of the control value after the repeated lower doses (Yamamoto et al. 1982).

When methyl parathion was given orally to rats at doses of 1.5 mg/kg and to guinea pigs at 50 mg/kg, plasma, erythrocyte, and brain cholinesterase activity was maximally inhibited within 30 minutes after administration. In rodents of both species that died after acute intoxication, brain cholinesterase levels decreased to 20% of control values and often to 5–7% (Miyamoto et al. 1963b). The species difference in susceptibility to orally administered methyl parathion is noted in Section 3.2.2.1.

Following acute oral toxicity from dosages ranging from 14 to 80 mg/kg, laboratory rats had earlier recovery of brain acetylcholinesterase levels than did feral cotton rats. Similar results were seen in a comparison of laboratory mice to feral mice (Roberts et al. 1988).

No cholinergic signs were seen in mice administered 6 mg/kg/day for 7–28 days (Crittenden et al. 1998). Brain acetylcholinesterase was significantly decreased at 3 and 6 (but not 1) mg/kg/day, and plasma cholinesterase was significantly decreased at 6 mg/kg/day.

Pregnant rats given methyl parathion orally at 1.5 mg/kg/day from day 6 to day 15 or 19 of gestation had cholinergic effects (Gupta et al. 1984). These effects were not seen at 1 mg/kg/day. Similarly, pregnant rats given methyl parathion orally at 1.5 mg/kg/day from day 6 through day 20 of gestation had

cholinergic signs, but those given 1 mg/kg/day did not (Gupta et al. 1985). At both dose levels, the dams had significant and dose-related depression of brain acetylcholinesterase activity and nondose-related decreases in brain muscarinic receptors. Effects in the fetuses and offspring are discussed in Section 3.2.2.5.

A study of three pesticides, administered separately, reported electrophysiological effects in male rats treated with methyl parathion through gavage administration to their dams during days 5–15 of gestation and days 2–28 of lactation at doses of 0.22, 0.44, or 0.88 mg/kg/day, followed by direct treatment of the male offspring in the same manner for 8 weeks, from weaning through 11–12 weeks of age. Dose-related changes on electrocorticograms of the somatosensory, visual, and auditory centers, on evoked potentials, and on tail nerve conduction velocity and refractory period were observed (Desi et al. 1998). The results were stated to be significantly different from controls at all three dose levels, but results specifically for methyl parathion were shown only for the electrocorticogram of the somatosensory area. No overt signs of toxicity were seen in the offspring. A minimal LOAEL of 0.22 mg/kg/day was identified from these experiments in which the rats were treated starting in the prenatal period and continuing though 12 weeks of age. Based on this value, an intermediate oral MRL of .0007 mg/kg/day was calculated as described in the footnote in Table 3-3.

In the same study (Desi et al. 1998), no significant effects on these end points were seen in male rats exposed to methyl parathion only through the treatment of their dams during gestation or gestation and lactation; these results are presented in Section 3.2.2.6.

Dogs receiving 0.12, 0.5, or 1.2 mg/kg/day methyl parathion in their diet for 12 weeks had reduced erythrocyte cholinesterase levels: 65% of baseline values for the 0.5-mg/kg/day group and 60% of baseline values for the 1.2-mg/kg/day group (Williams et al. 1959). Cholinesterase values in dogs fed 0.12 mg/kg/day in the diet did not differ significantly from controls. Over an 8-week postexposure period, the erythrocyte cholinesterase levels in dogs in the two highest dose groups recovered approximately 1% per day. Study limitations included the use of only two dogs (one of each sex) per dose group, use of dogs from unspecified sources, no discussion of clinical signs (if any), and no correlation of reduced cholinesterase values with general effects on the dogs' health.

A dose-response relationship was noted in dogs exposed to 0.03, 0.3, or 3.0 mg/kg/day methyl parathion in the diet for 13 weeks (Daly 1989). Significant reductions in erythrocyte cholinesterase activity (20–23%) and cholinesterase activity in the pons and cerebellum of the brain (43–54%) occurred in dogs

that were given 3.0 mg/kg/day methyl parathion for 13 weeks. There were no effects on either erythrocyte or brain cholinesterase activities in dogs that were given either 0.03 or 0.3 mg/kg/day methyl parathion. Significant reductions (53–59%) in plasma cholinesterase also occurred in the high-dose females. This latter effect was observed in both low- and high-dose males, but not in males at the mid dose. Thus, the results in the low-dose males do not appear to be treatment related. There were no effects on cholinesterase activity in any of the exposure groups following a 30-day postexposure recovery period.

Routine gross and histopathological examinations revealed no treatment-related effects on the nervous system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). In addition, there were no treatment-related effects on cholinesterase activity in plasma, red blood cells, or brains in dogs under these exposure conditions. These data are in agreement with the NOAEL established above for dogs exposed to these levels for 13 weeks.

Slight tremor was noted during the first 3 weeks to 4 months of treatment in male and female rats that were exposed to 2.5 mg/kg/day methyl parathion for 2 years; however, this effect subsided as exposure continued (Suba 1984). This effect was not noted in rats exposed to either 0.025 or 0.25 mg/kg/day methyl parathion. Abnormal gait was consistently observed in 2–14 out of 60 of the high-dose female rats from week 19 to termination and in 1 high-dose male, but only at the beginning of the second year of exposure. In addition, one female exposed to 0.25 mg/kg/day exhibited this effect from week 77 until termination. This effect did not occur in the controls or the low-dose exposure group. The data are limited for each of these effects because statistical significance was not determined. Peripheral neuropathy of the proximal and distal sciatic nerve in male and female rats was found to be related to chronic exposure to 2.5 mg/kg/day methyl parathion but not to 0.025 or 0.25 mg/kg/day methyl parathion (Suba 1984). Methyl parathion did not induce histopathological effects in the brain or spinal cord of treated animals. The pathology data are limited because statistical significance was not determined.

Mean plasma, erythrocyte, and brain cholinesterase activities were significantly reduced by 67–88%, 9–20%, and 76–79%, respectively, in rats of both sexes following 2-year exposures to 2.5 mg/kg/day methyl parathion (Suba 1984). This effect did not occur in rats exposed to either 0.025 or 0.25 mg/kg/day methyl parathion.

All reliable LOAEL values for neurological effects in rats for the acute-duration category, the highest NOAEL and all reliable LOAEL values in dogs for the intermediate-duration category, and the highest

NOAEL and all reliable LOAEL values in dogs and rats for the chronic-duration category are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

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

Methyl parathion has not been shown to be toxic to male germ cells in mice exposed to the chemical in the diet or drinking water in three studies discussed in Section 3.2.2.7. An additional study, also discussed in Section 3.2.2.7, reported significantly increased numbers of abnormal sperm in male mice administered methyl parathion by gavage at relatively high doses. Routine gross and histopathological examinations revealed no treatment-related effects on the reproductive system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981).

The highest NOAEL value in dogs for reproductive effects for the chronic-duration category is recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental toxicity in humans after oral exposure to methyl parathion.

Placental transfer of methyl parathion was demonstrated following oral administration to pregnant rats 1–3 days before parturition (Ackermann and Engst 1970).

In a study of the effects of methyl parathion on protein synthesis, rats were given 1 mg/kg/day of methyl parathion in a small amount of peanut butter (eaten within 2 minutes) or 1.5 mg/kg methyl parathion by gavage in peanut oil starting on day 6 of gestation and continuing through day 15 or 19. These exposures inhibited incorporation of ^{14}C valine into protein in maternal, placental, and fetal tissues (Gupta et al. 1984). A dose-related inhibition was observed in maternal brain, viscera, placenta, and whole embryos in rats on day 15 and in fetal brain and viscera on day 19. The inhibitory effect of methyl parathion on protein synthesis was greater on day 19 than on day 15 of gestation and was more pronounced in fetal than in maternal tissues. No signs of maternal toxicity were seen at 1 mg/kg/day. Signs of cholinergic stimulation, including muscle fasciculation, tremors, and mild clonic convulsions, were seen in some of

the dams at 1.5 mg/kg/day, maternal body weight gains were slightly but significantly depressed, and resorptions were increased. No gross structural abnormalities were found in the fetuses. This study is limited in that it did not adequately examine whether reduction in protein synthesis during the prenatal period would cause adverse effects in the offspring. The purity of the compound was also not reported.

In a follow-up study, pregnant rats were given 1 or 1.5 mg/kg/day of methyl parathion on days 6–20 of gestation (Gupta et al. 1985) in the same manner as in the previous study. Exposure to 1 mg/kg/day caused significant but small and transient reductions in maternal and fetal brain acetylcholinesterase activity, an increase in maternal but not fetal brain choline acetyltransferase activity, and a decease in maternal but not fetal muscarinic receptors. No visible signs of maternal or fetal toxicity were observed. Exposure to 1.5 mg/kg/day, on the other hand, significantly reduced acetylcholinesterase activity and increased choline acetyltransferase activity in the maternal brain and in all fetal brain regions at various stages during development. Muscarinic receptors were decreased in maternal but not fetal brains. Signs of cholinergic stimulation were seen in some of the dams. A slight but significant reduction in maternal weight gain and an increased incidence of fetal resorptions were also observed at 1.5 mg/kg/day. No gross structural abnormalities or changes in brain morphology were found in the fetuses. Impairment of behavior (decreased latency for cage emergence, reduction in accommodated locomotor activity, impairment of operant behavior) was found in 2–6-month-old offspring of rat dams fed methyl parathion at 1 mg/kg/day in peanut butter, but not in offspring of those administered 1.5 mg/kg/day in oil by gavage. The observed differences may have been caused by the differences in method and vehicle of administration, or potential nonlinearity in the dose-response for behavioral effects. Several other behavioral end points, measured in the offspring at various times from 1 day to 6 months of age, were not affected at either dose level.

Similar results for rats were reported by Crowder et al. (1980). Oral administration of 1 mg/kg/day of methyl parathion (99.9% purity) in corn oil on days 7–15 of gestation resulted in increased mortality in pups, relative to controls. Significant difference from controls in a maze transfer test was observed in pups from the treated group. However, use of a single-dose level precluded the assessment of dose-response, and several other behavioral end points were not affected. Furthermore, no information was presented regarding body weights or signs of toxicity in the treated dams.

Gavage administration of 1.5 mg/kg/day of methyl parathion to rats on days 6–15 of gestation resulted in increased resorptions, decreased fetal body weight, and hemorrhagic spots in the brain ventricles and skin

of the upper body of some of the fetuses (Kumar and Devi 1996). The data for hemorrhagic spots in the brain and skin were presented and analyzed for statistical significance as percent affected fetuses/total fetuses in dose group rather than percent per litter. Maternal toxicity (cholinergic signs and slight but significant depression of body weight gain) and significantly decreased placental weight and amniotic fluid weight were seen at 1.5 mg/kg/day.

In a study of three pesticides, the 11–12-week-old male offspring of rat dams administered methyl parathion at 0.22, 0.44, or 0.88 mg/kg/day on days 5–15 of gestation by gavage in an aqueous vehicle had no statistically significant changes in electrocorticograms, evoked potentials, or tail nerve conduction velocity or refractory period (Desi et al. 1998). A similar lack of significant effect was seen in male offspring of dams treated in the same manner during gestation and from the second day after delivery until weaning of the offspring at 4 weeks of age. There were slight trends in these indices, consistent in direction with the results obtained when treatment of the offspring was continued after weaning (see next paragraph). The electrocorticograms and evoked potentials studied by Desi et al. (1998) are more sensitive than the behavioral end points studied by Gupta et al. (1984, 1985) and Crowder et al. (1980), the doses were similar (0.88 mg/kg/day versus 1 mg/kg/day), and the period between dosing and testing was similar. The above findings by Desi et al. (1998), therefore, do not corroborate the findings in the other two studies. Whether the exposure vehicle contributed to the different outcomes is uncertain.

In the male offspring whose treatment was continued through 11–12 weeks of age, however, dose-related effects were seen on all the above end points, and these effects were significantly different from controls at all three dose levels (Desi et al. 1998) (see also Section 3.2.2.4). The study did not determine the critical period (if any) and duration of exposure for these neurological effects. A limitation of this study is that results specifically for methyl parathion were shown only for the somatosensory electrocorticogram; the other results for this chemical were stated in the text, but not shown.

No dose-response relationship can be established for the developmental toxicity of methyl parathion from the available database. All reliable LOAEL values in rats for developmental effects for the acute- and intermediate-duration categories are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located regarding carcinogenic effects in humans after oral exposure to methyl parathion.

There are two studies that describe negative carcinogenesis of methyl parathion administered orally to rodents. Methyl parathion was given in the diet to F344 rats and B6C3F_1 mice for 105 weeks (NCI 1979). Methyl parathion dosages were as follows: 0, 1, and 2 mg/kg/day for rats; 0, 8, and 16.2 mg/kg/day for female mice; and time-weighted average of 4.5 and 9.7 mg/kg/day for male mice. Time-weighted averages were used for male mice because methyl parathion dosages had to be adjusted downward after week 37 due to decreased mean body weight gain. A comprehensive set of tissues was examined by microscopy and gross necropsy. Study limitations included matched control groups for both species that were smaller (n=20) than methyl parathion dosage groups (n=50), dose adjustments during the study, and a significant increase in mortality in high-dose female rats (only 46% survived to study termination compared to 82% survival of low-dose females and 95% survival of control females). There were no lesions associated with the increased mortality. Under conditions of the bioassay, methyl parathion was not carcinogenic in rats or mice of either sex. Also, there were no noncancer systemic effects associated with methyl parathion exposure in rats or mice. In the second study, no treatment-related benign or malignant neoplasms were observed in rats following 2-year exposures to either 0.025, 0.25, or 2.5 mg/kg/day methyl parathion in the diet (Suba 1984).

3.2.3 Dermal Exposure

3.2.3.1 Death

Death in humans related to a combination of inhalation and dermal exposure was discussed in Sections 3.2.1.1 and 3.2.2.1.

LD_{50} values for the dermal route of exposure to methyl parathion have been established in acute studies for rats: 67 mg/kg for males and females (Gaines 1960), 110 mg/kg for males, and 120 mg/kg for females (EPA 1978e). The LD_{50} in male mice exposed by dermal application of methyl parathion to their hind feet (rather than shaved backs) was 1,200 mg/kg (Skinner and Kilgore 1982a). The mice were muzzled to prevent oral exposure from grooming.

The reliable LD_{50} values for rats and mice for the acute-duration category are recorded in Table 3-4.

Table 3-4. Levels of Significant Exposure to Methyl Parathion - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
				Less serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE							
Death							
Rat	once				67	(LD_{50})	Gaines 1960
Mouse	once				1200 M	(LD_{50})	Skinner and Kilgore 1982a
Systemic							
Rat	once	Cardio			67	(bradycardia; arrhythmia myocardial ischemia; complex heart block)	Galal et al. 1975

Cardio = cardiovascular; LD_{50} = Lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; mg/kg/day = milligram per kilogram per day; NOAEL = no-observable-adverse-effect level

3.2.3.2 Systemic Effects

No studies were located in humans or animals regarding respiratory, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects after dermal exposure to methyl parathion.

Cardiovascular Effects. No studies were located in humans regarding cardiovascular effects after dermal exposure to methyl parathion. Rats exposed dermally to the LD_{50} of 67 mg of methyl parathion/kg or to a one-half-LD_{50} dose developed abnormalities in their heart rate and electrocardiograms (Galal et al. 1975). Bradycardia occurred by 1 hour after dosing with a severe effect at 2 hours after dosing (91% reduction in rate in the LD_{50} group and 70% reduction in rate in the one-half-LD_{50} group). Arrhythmia and electrocardiographic abnormalities were pronounced in rats receiving the dermal LD_{50} dose of methyl parathion.

Dermal Effects. Based on a skin patch test, allergic (contact) dermatitis to methyl parathion occurred in a farmer (Lisi et al. 1987).

No studies were located regarding dermal effects in animals after dermal exposure to methyl parathion.

3.2.3.3 Immunological and Lymphoreticular Effects

A single case report of skin allergy to methyl parathion has been reported in humans (Lisi et al. 1987). Also see Section 3.2.3.2.

No studies were located regarding immunological effects in animals after dermal exposure to methyl parathion.

3.2.3.4 Neurological Effects

Mental disturbances, manifested as psychiatric sequelae, have been reported after exposure to organophosphates, including methyl parathion. Neuropsychiatric symptoms occurred in two aerial applicators, one of whom used methyl parathion as well as other insecticides, including chlorinated insecticides. One of these pilots had high levels of exposure to methyl parathion, toxaphene, and Dipterex® with saturation of his clothing when the tank of his aircraft accidentally overflowed (Dille and Smith 1964). Several

months after the accident, the subject complained of dizziness, anxiety, emotional lability, frequent and severe disagreements with family and associates, and inability to perform familiar tasks.

Erythrocyte cholinesterase levels were monitored in two men exposed dermally to methyl parathion after entering a cotton field that had been sprayed with this pesticide (Nemec et al. 1968). The field was entered on two separate occasions: twice within 2 hours after an ultra-low-volume spraying and a third time within 24 hours after spraying. Dermal methyl parathion residues 2 hours after spraying were 2–10 mg on the arms; dermal residues 24 hours after spraying were 0.16–0.35 mg on the arms. The exposed individuals did not have signs of cholinergic toxicity, but erythrocyte cholinesterase levels after the third exposure were 60–65% of preexposure levels.

Mice that were exposed dermally to residues of methyl parathion in emulsifiable concentrate on foliage, and were muzzled to prevent oral intake, developed inhibition of plasma cholinesterase and erythrocyte cholinesterase after two 10-hour exposures (Skinner and Kilgore 1982b). For the organophosphate pesticides tested in this study, cholinergic signs generally were seen in mice with cholinesterase inhibition >50%; results for this end point were not broken down by pesticide.

In male mice in the dermal LD_{50} study described under lethality, the ED_{50} values (doses at which adverse effects were observed in 50% of the treated animals) for plasma and red blood cell (RBC) cholinesterase inhibition in survivors were 950 and 550 mg/kg, respectively, compared to a dermal LD_{50} of 1,200 mg/kg (Skinner and Kilgore 1982a). The hind feet of the mice were exposed to the pesticide, and the mice were muzzled to prevent oral exposure from grooming. Because these ED_{50} values were obtained in surviving mice in a 24-hour LD_{50} study, they were based on a resistant population, and are not considered suitable for inclusion in the LSE tables and figures.

3.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans and animals after dermal exposure to methyl parathion.

3.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans and animals after dermal exposure to methyl parathion.

3.2.3.7 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to methyl parathion.

3.2.4 Other Routes of Exposure

Ocular effects consisting of electroretinographic changes occurred in mice exposed by the intraperitoneal route to an LD_{50} dose or a dose equal to half of an LD_{50} dose of methyl parathion (Carricaburu et al. 1980). These changes were a direct effect of methyl parathion on repolarization of retinal photo-receptors. Rats, injected intraperitoneally with methyl parathion, developed cholinergic signs at dosage levels as low as 1.0 mg/kg/day for 7 days (Hasan and Khan 1985; Khan and Hasan 1988). Exposed rats had alterations in brain structural components with an increase in brain lipid, phospholipid, and cholesterol content in various portions of the brain (Hasan and Khan 1985) and depletion of gangliosides and glycogen (Khan and Hasan 1988). Lipid peroxidation was increased in the cerebrum but inhibited in the hindbrain (Hasan and Khan 1985). These changes in brain structural components suggest another type of toxic change induced by methyl parathion in the nervous system that could also be responsible for some of the acute and chronic neurologic effects seen in humans. Whether such effects could occur in humans exposed to low levels of methyl parathion that did not produce overt toxicity is unknown. Assays for estrogenic activity of intraperitoneally injected methyl parathion in hemi-ovariectomized rats indicated some interference with compensatory ovarian hypertrophy, but a lack of typical estrogenic activity (Asmathbanu and Kaliwal 1997; Dhondup and Kaliwal 1997). Fetotoxicity and offspring with altered brain enzymes and impaired behavior have been reported in rats after oral or parenteral maternal administration of methyl parathion at doses that inhibited acetylcholinesterase activity and, in some studies, produced cholinergic signs in the dams (Crowder et al. 1980; Fish 1966; Gupta et al. 1985; Tanimura et al. 1967). Pregnant female mice exposed to 60 mg/kg methyl parathion by the intraperitoneal route had significantly increased incidences of fetuses with cleft palate and dose-related increases in fetal deaths, compared to control litters (Tanimura et al. 1967). Significant increases in abnormal sperm morphology were seen in mice following intraperitoneal injection of methyl parathion at a dose level of 6 mg/kg (Pagulayan et al. 1994).

3.3 GENOTOXICITY

In a case-control study of pesticide factory workers in Brazil exposed to methyl parathion and formulating solvents, the incidence of chromosomal aberrations in lymphocytes was investigated (De Cassia Stocco et al. 1982). Though dichlorodiphenyltrichloroethane (DDT) was coformulated with methyl parathion, blood DDT levels in the methyl parathion-examined workers and "nonexposed" workers were not significantly different. These workers were presumably exposed to methyl parathion via both inhalation and dermal routes; however, a dose level was not reported. The exposed workers showed blood cholinesterase depressions between 50 and 75%. However, the baseline blood cholinesterase levels in nonexposed workers were not reported. No increases in the percentage of lymphocytes with chromosome breaks were found in 15 of these workers who were exposed to methyl parathion from 1 week to up to 7 years as compared with controls. The controls consisted of 13 men who had not been occupationally exposed to any chemical and were of comparable age and socioeconomic level. This study is limited because of concomitant exposure to formulating solvents, the recent history of exposure for the workers was not reported, the selection of the control group was not described adequately, and the sample size was limited.

Chromosome aberrations were detected in lymphocytes of individuals acutely intoxicated by methyl parathion by the inhalation route (Van Bao et al. 1974). Blood samples were taken 3–6 days after exposure and again at 30 and 380 days. A temporary but significant ($p<0.05$) increase was noted in the frequency of stable chromosomal aberrations in the exposed individuals. The study limitations include small sample size, absence of a control group, lack of quantification of exposure levels, and a possible concomitant exposure to other substances via the dermal route.

No studies were located regarding genotoxic effects in animals after inhalation exposure to methyl parathion.

The lymphocytes from 31 patients exposed to various organophosphate pesticides were examined for chromosomal aberrations (Van Bao et al. 1974). Five of the patients were exposed to methyl parathion only. Blood samples were taken 3–6 days after exposure and again at 30 and 180 days. A significant ($p<0.05$) increase was noted in the frequency of stable chromosomal aberrations in acutely intoxicated persons (although such cells are eventually lost from the cell population). Two of the methyl parathion-exposed persons had taken large doses orally in suicide attempts. The study limitations include small sample size, absence of a control group, lack of quantification of exposure levels, and possible

concomitant exposure to other substances via the dermal route. Although the study did not quantify the exposure levels, the results suggest that methyl parathion can exert direct genotoxic effects on chromosomes.

In a similar study, the lymphocytes from five patients who ingested methyl parathion (Wofatox) in suicide attempts were examined for aneuploidy, chromatid aberrations, and chromosome aberrations (Czeizel 1994). No significant differences from the 15 control patients were seen in these end points. The controls were patients who had undergone appendicitis or hernia surgery, and were matched for sex, age, and socioeconomic status with a larger set of 31 pesticide poisoning cases, of which the methyl parathion cases were a subset. Limitations of this study include the small number of methyl parathion cases, and the use of appendicitis and other surgery patients as controls.

Methyl parathion administered to male mice in the diet or drinking water did not increase the incidence of resorption of fetuses in mated dams (Degraeve et al. 1985; Waters et al. 1982). In mice, dietary exposure to the maximum tolerated dose, and one-half and one-quarter of the maximum tolerated doses failed to produce preimplantation embryo loss from the resultant matings with untreated females (Waters et al. 1982). However, no specific details regarding the actual doses administered were provided by the authors. The findings of these two studies were also supported by the absence of a dominant-lethal effect in mice receiving 0.026 mg/kg/day of methyl parathion in drinking water for 7 weeks (Degraeve et al. 1984a). This result suggests that methyl parathion is not toxic to male mouse germ cells. However, relatively high levels of methyl parathion can result in changes in sperm morphology. Male mice, orally exposed (gavage) to doses in the range of 9.375–75 mg/kg, exhibited dose-related significantly increased percentages of abnormal sperm at all doses (Mathew et al. 1992). Significant increases in abnormal sperm morphology were also seen in mice following intraperitoneal injection of 6 mg /kg, but not 1.3 mg/kg (Pagulayan et al. 1994). Of two studies in *Drosophila melanogaster*, one (Tripathy et al. 1987) showed mutagenic effects in somatic and germ cell lines and induction of sex-linked recessive lethals, whereas the other one (Waters et al. 1982) provided negative results.

Methyl parathion has been tested in numerous genotoxicity assays using prokaryotic and eukaryotic systems with both positive and negative results. Results of these studies are summarized in Tables 3-5 and 3-6.

When methyl parathion was tested in *Salmonella typhimurium*, contradictory results were reported with or without using metabolic activation (Rashid and Mumma 1984; Shigaeva and Savitskaya 1981; Waters

Table 3-5. Genotoxicity of Methyl Parathion *In Vivo*

Species (test system)	End point	Results	Reference
Eukaryotic organisms:			
Drosophila melanogaster/males	Recessive lethal	–	Waters et al. 1982
D. melanogaster/dietary exposure	Recessive lethal somatic mutation	+	Tripathy et al. 1987
Mammalian cells:			
Rat bone marrow/intraperitoneal injection	Induction of micronuclei	+	Grover and Malhi 1985
Mouse/oral exposure; diet or drinking water	Dominant lethal	–	Degraeve et al. 1985; Waters et al. 1982
Mouse/oral exposure; drinking water	Chromosomal aberrations	–	Degraeve et al. 1985
Mouse/intraperitoneal administration	Chromosomal aberrations	–	Huang 1973
Mouse/oral exposure; gavage	Sperm shape abnormalities	+	Mathew et al. 1992
Human lymphocytes/dermal and inhalation exposure	Chromosomal aberrations	–	De Cassia Stocco et al. 1982
Human lymphocytes/oral exposure	Chromosomal aberrations	+	Van Bao et al. 1974
Human lymphocytes/oral exposure	Chromosomal aberrations	–	Czeizel 1994

– = negative result; + = positive result; (+) = weakly positive result

Table 3-6. Genotoxicity of Methyl Parathion *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Bacteria:				
Salmonella typhimurium/plate incorporation	Reverse mutation	–	–	Waters et al. 1982
		+	–	Rashid and Mumma 1984
		No data	+	Shigaeva and Savitskaya 1981
Escherichia coli/WP2;plate incorporation	Reverse mutation	–	–	Dean 1972; Waters et al. 1982
E. coli/K-12 COIE/plasmid DNA	DNA damage	No data	+	Griffin and Hill 1978
E. coli/plate incorporation	5-Methyltryptophan resistance	No data	+	Mohn 1973
Eukaryotic organisms:				
Yeast:				
Saccharomyces cerevisiae (D7)/plate incorporation	Reverse mutation	–	–	Waters et al. 1982
S. cerevisiae (D3)/plate incorporation	Mitotic recombination	No data	+	Waters et al. 1982
S. cerevisiae (D7)/spot test	Gene conversion	–	–	Waters et al. 1982
S. typhimurium	DNA damage	No data	+	Rashid and Mumma 1984
Mammalian cells:				
Chinese hamster ovary	Sister chromatid exchange	+	–	Waters et al. 1982
Chinese hamster V79	Sister chromatid exchange	No data	+	Chen et al. 1981
Human lymphoid cells/LAZ-007	Sister chromatid exchange	No data	+	Sobti et al. 1982
Human lymphocytes	Sister chromatid exchange	No data	+	Chen et al. 1981; Gomez-Arroyo et al. 1987
Burkitt lymphoma/835M	Sister chromatid exchange	No data	+	Chen et al. 1981
Human lymphocytes	Chromosomal aberrations	No data	+	Kumar et al. 1993

Table 3-6. Genotoxicity of Methyl Parathion *In Vitro (continued)*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Human hematopoietic cells/RPMI 1788, 7191; B411-4	Chromosomal damage	No data	–	Degraeve et al. 1985; Huang 1973
Human lung fibroblasts	Unscheduled DNA synthesis	–	–	Waters et al. 1982

– = negative result; + = positive result; DNA = deoxyribonucleic acid

et al. 1982). However, it tested negative in *Saccharomyces cerevisiae* strain D7 for both reverse mutation and gene conversion (Waters et al. 1982) and in *Escherichia coli* WP 2 for reverse mutation (Dean 1972). Methyl parathion treatment resulted in a negative response for reverse mutation (Waters et al. 1982) but a positive response for 5-methyl tryptophan resistance assay (Mohn 1973) in *E. coli*. Positive results were also reported for mitotic recombination in *S. cerevisiae* D3 (Waters et al. 1982) and for deoxyribonucleic acid (DNA) damage in *S. typhimurium* (Rashid and Mumma 1984) and *E. coli* (Griffin and Hill 1978). Methyl parathion gave a negative response for unscheduled DNA synthesis in cultured human lung fibroblasts (Waters et al. 1982).

Results of methyl parathion assays involving effects on chromosomes have also been contradictory. For sister chromatid exchange, Waters et al. (1982) reported a positive response in Chinese hamster ovary cells only in the presence of metabolic activation system, while methyl parathion tested positive without a metabolic activation system in Chinese hamster V79 cells (Chen et al. 1981), cultured normal human lymphoid cells (Chen et al. 1981; Gomez-Arroyo et al. 1987; Sobti et al. 1982), and Burkitt's lymphoma cells (Chen et al. 1981). Chen et al. (1981) found a significant dose-related increase in sister chromatid exchange in both hamster and human cultured cells, but dose-related cell cycle delays were less pronounced in human cell lines than in V79 cells. Negative results were obtained for chromosomal aberrations in human lymphocytes without a metabolic activation system (Kumar et al. 1993).

Induction of micronuclei has been reported in bone marrow cells of rats injected intraperitoneally with methyl parathion (Grover and Malhi 1985). Although negative results were obtained for chromosomal aberrations in mouse cells and human hematopoietic cells (Degraeve et al. 1984a; Huang 1973), contradictory results were reported in human lymphocytes following exposure of humans to methyl parathion (Czeizel 1994; De Cassia Stocco et al. 1982; Van Bao et al. 1974). Exposure to other compounds complicates interpretation. In the dominant lethal assay, no increase in the incidence of pre- or postimplantation fetal lethality was found in the litters of male mice following oral exposure (Degraeve et al. 1985; Jorgensen et al. 1976; Waters et al. 1982), but an assay for sperm shape abnormalities yielded positive results at relative high oral doses (Mathew et al. 1992). Thus, the available evidence is inconclusive, and no determination regarding the potential genotoxic risks of methyl parathion exposure for humans can be made.

3.4 TOXICOKINETICS

Methyl parathion can be readily absorbed by humans following inhalation, oral, or dermal exposure, although quantitative data are lacking. Studies in animals indicate that oral absorption following single doses can amount to 80% of the administered dose within a few days of dosing. A single dermal study in rats also suggested almost complete absorption of an applied dose within a 96-hour period. No data are available regarding pulmonary absorption of methyl parathion in animals. Methyl parathion was found to be widely distributed in organs and tissues of rats following dermal exposure, but first-pass metabolism greatly limits its distribution following oral absorption. Methyl parathion has been detected in human breast milk and studies in animals have shown that it can cross the placenta and be transferred to the fetus. Methyl parathion is rapidly and extensively metabolized, mainly in the liver, to polar substances that are quickly excreted in the urine. Oxidative desulfuration by microsomal oxidases transforms methyl parathion into the neurotoxic, active metabolite, methyl paraoxon; the specific isozyme involved in this reaction has not been identified. Other reactions including oxidation, hydrolysis, dearylation, and dealkylation detoxify methyl parathion. A major detoxification pathway is enzymatic hydrolysis of methyl paraoxon to dimethyl phosphate and 4-nitrophenol. These metabolites are eliminated primarily in the urine in humans, rats, and mice.

3.4.1 Absorption

Often, absorption occurs by multiple routes in humans. Dean et al. (1984) reported deaths and toxic effects as well as lowered blood cholinesterase levels and excretion of urinary 4-nitrophenol in several children who were exposed by inhalation, oral, and possibly dermal routes after the spraying of methyl parathion in a house. In the same incident (Dean et al. 1984), absorption was indicated in adults who also excreted 4-nitrophenol in the urine, though at lower levels than some of the children, and in the absence of other evidence of methyl parathion exposure. In this study, the potential for age-related differences in absorption rates could not be assessed because exposure levels were not known and the children may have been more highly exposed than the adults. Health effects from multiple routes are discussed in detail in Section 3.2.

3.4.1.1 Inhalation Exposure

No studies were located regarding absorption in humans and animals after inhalation exposure to methyl parathion. However, it can be concluded that pulmonary absorption occurred in humans as evidenced by

toxic systemic effects found in humans dying after acute inhalation exposure to methyl parathion (Fazekas 1971).

3.4.1.2 Oral Exposure

Absorption following acute oral exposure is indicated in a study in which four volunteers received methyl parathion once a day with food for 5 consecutive days (Morgan et al. 1977). Urine was collected for 24 hours after each dose and for 2 days after the last dosing day. The average 24-hour excretions of the metabolites 4-nitrophenol and dimethyl phosphate following each dose accounted for 27 and 12% of the ingested dose, respectively. The highest rate of excretion for 4-nitrophenol occurred during the first 4 hours after dosing, and for dimethyl phosphate, occurred during in the interval from 4 to 8 hours after dosing. These results indicate rapid absorption.

Rapid and efficient absorption in animals follows oral administration of methyl parathion (Braeckman et al. 1983; Hollingworth et al. 1967). Oral absorption was 77 and 79% in two dogs receiving 3 mg/kg of ^{35}S-labeled methyl parathion by gavage (Braeckman et al. 1983). This conclusion was based on a comparison of the 6-day urinary excretion of radioactivity after gavage administration versus intravenous injection. In mice, 80% of the radioactivity from a gavage dose of 3 mg/kg of ^{32}P-labelled methyl parathion was recovered as radiolabeled metabolites in the urine, and up to 10% was recovered in the feces at 72 hours (Hollingworth et al. 1967). Estimates of fecal excretion were considered unreliable. Therefore, based on 80% recovery in the urine, it can be concluded that at least 80% of the dose was absorbed following oral administration of methyl parathion. Approximately 75% of the urinary excretion occurred within the first 12 hours. Furthermore, decreased cholinesterase activity (Ceron et al. 1995; Miyamoto et al. 1963b) and detection of methyl parathion urinary metabolites (Chang et al. 1997; Youssef et al. 1987) after oral doses of methyl parathion provide indirect evidence of absorption in animals.

The data presented above suggest that methyl parathion would be absorbed by humans following ingestion of food and drinking water contaminated with methyl parathion. However, no data are available on the rate and extent of absorption in humans.

3.4.1.3 Dermal Exposure

Epidemiological studies indicate that absorption of methyl parathion occurs in humans following acute dermal exposure (Nemec et al. 1968; Ware et al. 1973, 1974, 1975). On two separate occasions, two entomologists were in a field for 5 minutes, 2 hours after it was sprayed with methyl parathion; 2–10 mg methyl parathion was measured on the skin of both arms (Nemec et al. 1968). A third exposure occurred 24 hours after spraying the field; levels of methyl parathion on the skin of the arms ranged from 0.163 to 0.351 mg methyl parathion. Blood cholinesterase levels after the three exposures were 60% of pre-exposure levels in these subjects, which suggests that absorption had occurred (Nemec et al. 1968). Two volunteers entered treated cotton fields for 30-minute periods at 0, 12, 24, 48, and 72 hours postexposure (Ware et al. 1973). Twenty-four hours after exposure, 0.027 and 0.032 mg/L methyl parathion were detected in the serum. The skin was considered to be the major route of exposure in this study (Ware et al. 1973). In five subjects, the amount of methyl parathion on the hands averaged 1.7 mg following 5 hours of exposure in fields that had been sprayed with methyl parathion 12 hours earlier (Ware et al. 1975). The amount of methyl parathion averaged 2.2 mg on the arms, 0.4 mg on the torso, 0.03 mg on the legs, 10.6 mg on the shirts, and 40.0 mg on the pants. The serum contained 70–227 ppb of methyl parathion 3–7 hours after the 5-hour exposure compared with 0–4 ppb at 24 hours. Serum levels were highest immediately after exposure (0.156 mg/L); after 48 hours, cumulative levels of urinary 4-nitrophenol varied between 1.1–23 mg.

Although the extent of absorption was not measured, the above evidence suggests that absorption in humans occurs rapidly following dermal exposure to commercial pesticide formulations of methyl parathion.

In a study of pregnant rats exposed to 10 mg/kg of radiolabeled methyl parathion (in acetone) that was applied to the back of the neck (unoccluded), approximately half of the dose was absorbed within 1 hour postapplication, and 95% was absorbed within 96 hours. Skin disappearance rate constants of 0.35 $hour^{-1}$ and 0.03 $hour^{-1}$ were estimated, and corresponded to half-lives of 2 and 22 hours, respectively (Abu-Quare et al. 2000). Although animals were housed individually, the possibility of some degree of oral absorption could not be discounted. Additional evidence of dermal absorption comes from the finding of inhibition of plasma cholinesterase activity in mice following dermal exposure to methyl parathion (Skinner and Kilgore 1982b).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals after inhalation exposure to methyl parathion. Although cases of inhalation exposure have been reported, there were no data that provided detailed information on the distribution of methyl parathion residues in various tissues.

3.4.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to methyl parathion.

Following a single gavage administration of 20 mg/kg methyl parathion, the highest serum concentration reported in dogs ranged from 0.13 to 0.96 µg/mL 3–9 hours postexposure (Braeckman et al. 1983). The low systemic availability of methyl parathion following oral gavage in dogs was suggested to be the result of hepatic first-pass metabolism (Braeckman et al. 1983).

Placental transfer of methyl parathion was demonstrated following oral administration to pregnant rats 1–3 days before parturition (Ackermann and Engst 1970). Thirty minutes after administration, methyl parathion was found in fetal brain, liver, and muscle, and in the placenta and maternal liver, suggesting its rapid distribution. The fetal liver concentration of methyl parathion was nearly 2-fold that of the maternal liver and approximately half of the concentration found in the placenta. Small amounts of methyl paraoxon, the oxidative metabolite of methyl parathion, were found in fetal brain, liver, and muscle, but could not be detected in maternal liver or placental tissue. Although the source of exposure was not determined, methyl parathion was detected in breast milk of 8/90 women tested in 5 of 10 regions of central Asia (Lederman 1996). Methyl parathion was not detected in the breast milk of mothers tested in the other 5 regions (Lederman 1996) or in breast milk of 11 Italians tested for the presence of a number of pesticides, including methyl parathion (Roggi et al. 1991). A study of a mixture of pesticides (methyl parathion, lindane, and permethrin) in rats reported that methyl parathion was present in higher concentrations in the dams' milk and in the pups' blood than in the dams' blood following oral exposure of the dams on lactation days 1–14 (Golubchikov 1991; Goncharuk et al. 1990). Confidence in these findings is low because descriptions of the methods and results were cursory.

The available data are insufficient to determine the pattern or extent of distribution in human tissues after oral exposure to this compound.

3.4.2.3 Dermal Exposure

There is limited information available regarding the distribution of methyl parathion after dermal exposure in humans. Two subjects, dermally exposed to methyl parathion, had 2.74 and 1.23 mg on their hands. Twenty-four hours after exposure, the serum levels were 0.027 and 0.032 mg/L, respectively (Ware et al. 1973). Twelve hours after cotton fields were sprayed, five men entered the treated fields for 5 hours. An average of 1.7 mg methyl parathion was detected on their hands. Serum concentrations averaged 0.156 mg/L in these subjects after 3 hours of exposure. Levels decreased to 0.1 and 0.002 mg/L at 2 and 24 hours postexposure, respectively (Ware et al. 1975). Although 0.5 mg methyl parathion was detected on the hands of four subjects, none was found in the serum (Ware et al. 1974). No information on the tissue distribution of methyl parathion in humans was found.

Following single dermal applications of 10 mg/kg of radiolabeled methyl parathion to pregnant rats, methyl parathion was found to be widely distributed to all major tissues and organs. Concentrations were highest in plasma and kidney, maximum levels measured 2 hours postapplication. Peak levels in liver, brain, fetus, and placenta, were measured 2 to 10 hours later, at which times the highest concentration of methyl parathion was in the fetus (Abu-Quare et al. 2000).

3.4.2.4 Other Routes of Exposure

Distribution of methyl parathion was rapid when it was administered intravenously to rats (3 and 15 mg/kg) and guinea pigs (20 and 40 mg/kg) (Miyamoto 1964). Levels were highest in the brain, liver, lungs, kidneys, and heart of these animals at 2.5 minutes postexposure (Miyamoto 1964). The levels of a metabolite, methyl paraoxon, were highest in the lungs and liver of guinea pigs, and in the liver of rats. However, it should be noted that the protein-bound oxygen analog was not measured in the study. Serum methyl parathion levels were highest in dogs immediately following intravenous exposure (Braeckman et al. 1980). The serum concentrations declined rapidly, followed by a slower clearance, beginning at 5 hours postexposure, for doses of 3, 10, or 30 mg/kg methyl parathion. Intraperitoneal injection of methyl parathion in pregnant rats has resulted in fetal toxicity, expressed in reduced fetal brain cholinesterase levels; this is another indication that methyl parathion and/or its toxic metabolite can cross the placental barrier (Fish 1966).

The protein binding of methyl parathion *in vitro* was 93% in dog serum and 94% in human serum (Braeckman et al. 1983). The protein binding of methyl parathion in a solution of human albumin that approximated the concentration of albumin in human serum also was 94%, suggesting that albumin is the main binding protein for methyl parathion in serum. Albumin probably acts as a transport protein, because although the degree of protein binding in serum is high, a high volume of distribution has been determined for methyl parathion in the dog (Braeckman et al. 1980, 1983).

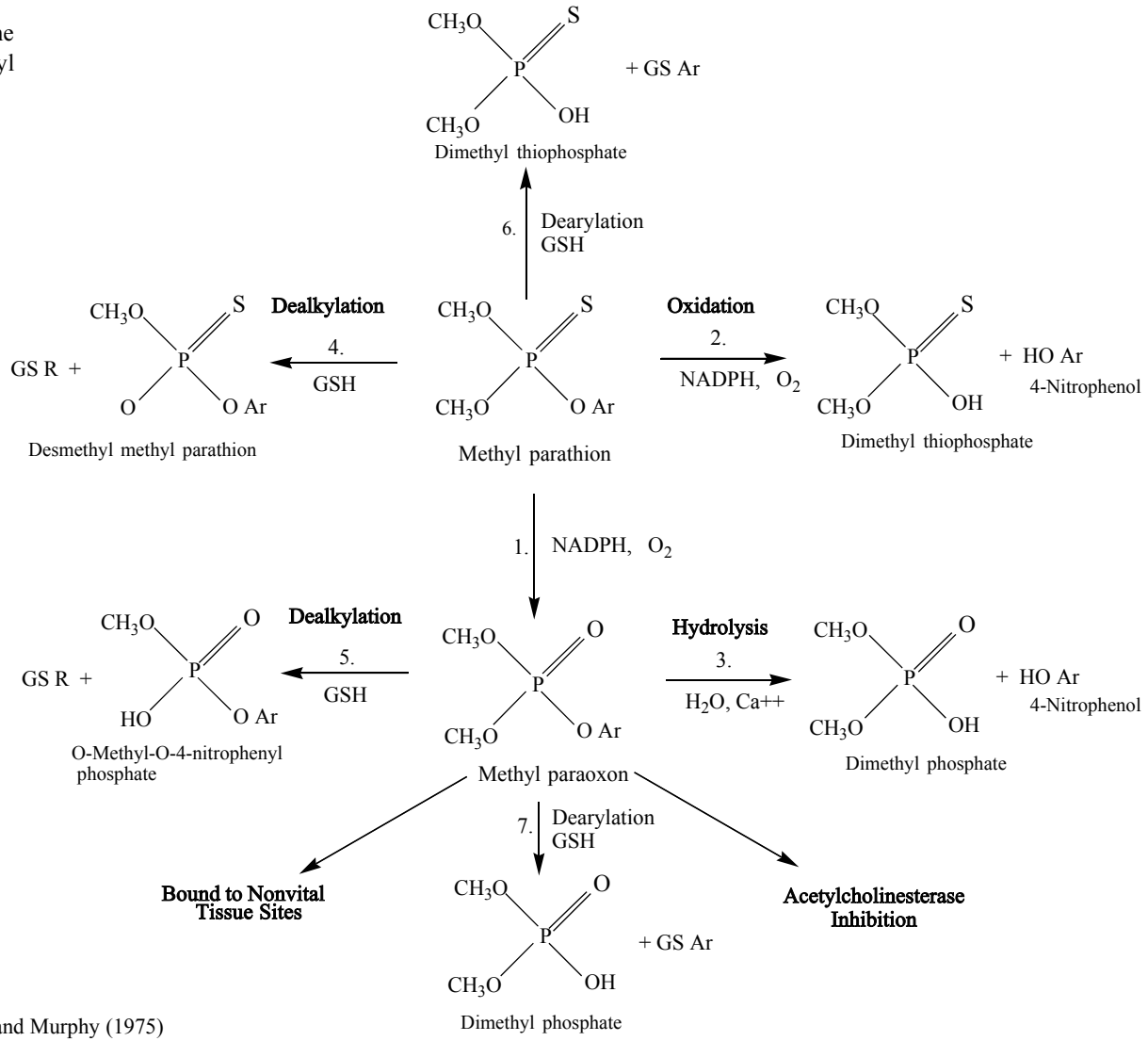
3.4.3 Metabolism

Methyl parathion is a phosphorothioate, which refers to the organophosphate compounds that contain the P=S substructure (Nakatsugawa et al. 1968). The metabolism of methyl parathion has been well studied *in vitro* using rat, mouse, rabbit, guinea pig, and human liver homogenates (Benke and Murphy 1975; Hollingworth et al. 1973; Nakatsugawa et al. 1968; Neal and DuBois 1965) and *in situ* using intact rat livers (Zhang and Sultatos 1991). Metabolism has also been studied *in vivo* using pregnant rats exposed by dermal application of radiolabeled methyl parathion (Abu-Qare et al. 2000). No metabolism studies were conducted by the inhalation route. The low systemic availability of methyl parathion after oral administration in dogs, and the high hepatic extraction ratios after intravenous administration, suggest first-pass metabolism by the liver (Braeckman et al. 1983). The proposed metabolic pathway based on the results of *in vitro* studies is shown in Figure 3-3 (Benke and Murphy 1975). This compound can be activated (oxidative desulfuration) to its toxic metabolite, methyl paraoxon, *in vitro* using mouse liver homogenates (Benke et al. 1974) and *in situ* (Zhang and Sultatos 1991) in rats (see reaction 1 in Figure 3-3). Methyl paraoxon has been found in liver and brain of rats following dermal exposure to methyl parathion (Abu-Qare et al. 2000). This intermediate oxygen analog is more potent than the parent compound in inhibiting cholinesterase enzyme activity and causing the neurotoxic effects of methyl parathion (Benke et al. 1974). This oxidative reaction requires microsomal oxidases, NADPH, and oxygen (Benke et al. 1974; Hollingworth et al. 1973; Nakatsugawa et al. 1968).

The detoxification of methyl parathion may occur through any of several metabolic processes (i.e., oxidation, hydrolysis, dearylation, and dealkylation) (Benke and Murphy 1975; Benke et al. 1974; Hollingworth et al. 1973; Nakatsugawa et al. 1968; Neal and DuBois 1965). A major detoxification pathway is enzymatic hydrolysis of the toxic metabolite, methyl paraoxon to dimethyl phosphate and 4-nitrophenol (reaction 3 in Figure 3-3) (Benke and Murphy 1975; Benke et al. 1974). In humans, rats, and mice, these nontoxic metabolites are eliminated primarily in the urine (Hollingworth et al. 1973; Morgan et al. 1977; Plapp and Casida 1958). Another detoxifying pathway (reaction 2) is the oxidation

Figure 3-3. Proposed Metabolic Pathways of Methyl Parathion

GSH = Glutathione
Ar = p-Nitrophenyl



*Adapted from Benke and Murphy (1975)
The numbered reactions (1-7) are reference numbers for pathways discussed in the text.

of the aryl group in the parent compound to produce dimethyl thiophosphate and 4-nitrophenol. The reaction occurs only in the presence of NADPH (Nakatsugawa et al. 1968) and has been studied in liver homogenates of rats, rabbits, mice, and guinea pigs (Benke et al. 1974; Nakatsugawa et al. 1968; Neal and Dubois 1965). Radiolabeled 4-nitrophenol has been detected in the liver of rats following dermal exposure to radiolabeled methyl parathion (Abu-Qare et al. 2000). Dimethyl thiophosphate has been detected in the urine of rats treated with methyl parathion (Plapp and Casida 1958). The 4-nitrophenol can be glucuronidated to form 4-nitrophenol glucuronide (Zhang and Sultatos 1991).

In vitro studies indicate that detoxification of methyl parathion and methyl paraoxon can occur by glutathione-dependent alkyltransferase and aryltransferase (Benke and Murphy 1975; Benke et al. 1974). Glutathione (GSH) alkyltransferase converts methyl parathion to desmethyl methyl parathion (reaction 4 in Figure 3-3), and methyl paraoxon to O-methyl-O-4-nitrophenol phosphate (reaction 5 in Figure 3-3). Glutathione aryltransferase produces dimethyl thiophosphate from methyl parathion (reaction 6 in Figure 3-3), and dimethyl phosphate from methyl paraoxon (reaction 7 in Figure 3-3) (Benke and Murphy 1975). The addition of glutathione in liver homogenates increases the disappearance of methyl parathion and methyl paraoxon in mice (Benke et al. 1974). Pretreatment with dimethyl maleate, which reduces glutathione levels, potentiated toxicity in mice (Mirer et al. 1977), but not in female rats (Chambers et al. 1994). Zhang and Sultatos (1991) did not detect methyl parathion-related glutathione conjugates in the effluent or bile of rat livers perfused *in situ* with 20–80 µM solutions of methyl parathion. Although the Mirer et al. (1977) study indicates that glutathione conjugation might be involved in detoxification of methyl parathion in mice, it should be noted that near lethal concentrations of methyl parathion were used in the intraperitoneal studies, and *in vitro* studies employed exposure levels higher than those likely to be encountered in sublethal *in vivo* toxicity studies. Glutathione-dependent metabolism of methyl parathion, therefore, may not be a significant detoxification pathway *in vivo* at sublethal toxic concentrations in which access to glutathione *S*-transferases might be concentration limited (Huang and Sultatos 1993).

Methyl paraoxon may also be made unavailable by binding to noncritical tissue and plasma constituents (Benke and Murphy 1975), including cholinesterase (Parkinson 1996). In addition, the parent compound is bound to albumin, in serum, as discussed previously in Section 3.4.2.4, but this binding does not appear to limit the availability of methyl parathion to the tissues, indicating that it is reversible. Tissue binding appears to be more important than serum binding (Braeckman et al. 1980, 1983).

The relative rates of activation and detoxification of methyl paraoxon within the liver determine whether net activation or detoxification will occur (Sultatos 1987). Sex-differences have been observed in acute

LD_{50} values for methyl parathion (see Section 3.2.2.1). The lower LD_{50} values in male (compared to female) rats may possibly be attributed to enhanced activation of thio-organophosphate pesticides in the liver of male rats as reported by Murphy and DuBois (1958). Acute intraperitoneal LD_{50} values in male and female rats increase with increasing postpartum age, up to approximately 35–40 days for males and 60 days for females (Benke and Murphy 1975). It has also been found that the metabolism of methyl parathion is affected by the age of rats (Benke and Murphy 1975). The age-related ratios of oxidative deactivation (reaction 2 in Figure 3-3) to oxidative activation (reaction 1) of methyl parathion correlated with the LD_{50} values better than did either measure alone. In addition, age-related increases in hydrolysis (reaction 3), glutathione-dependent dealkylation and dearylation (reactions 5 and 7), and tissue binding of methyl paraoxon correlated with the increase in LD_{50} values (Benke and Murphy 1975), indicating that detoxification pathways for methyl parathion may be more effective in 60-day-old rats than in younger ones (Benke and Murphy 1975). However, at present, mechanisms relating to increased susceptibility of immature rats relative to adults are not fully understood.

3.4.4 Elimination and Excretion

4-Nitrophenol and 4-nitrophenol glucuronide are excreted in urine. The studies of urinary excretion of methyl parathion metabolites, including those reported in this section, generally hydrolyze the glucuronide prior to analysis and report the resulting total 4-nitrophenol values.

3.4.4.1 Inhalation Exposure

Most of the toxic effects caused by methyl parathion resulted from exposure by multiple routes, especially for workers in sprayed fields or formulating facilities, or people in homes. Dean et al. (1984) reported deaths and toxic effects in several children as well as lowered blood cholinesterase levels and excretion of urinary 4-nitrophenol (adults showing no adverse effects also excreted 4-nitrophenol). Health effects from multiple routes have been discussed in detail in Section 3.2.

No studies were located regarding excretion in animals after inhalation exposure to methyl parathion.

3.4.4.2 Oral Exposure

Limited information was available regarding excretion in humans after oral exposure to methyl parathion. During 5 days of exposure of four subjects to 2 or 4 mg of methyl parathion once daily in food (0.028 or

0.057 mg/kg/day), the average 24-hour excretions of the metabolites dimethyl phosphate and 4-nitrophenol accounted for 27 and 12% of the administered dose, respectively (Morgan et al. 1977). An average of 60 and 86% of the total urinary excretion of 4-nitrophenol had been eliminated at 4 and 8 hours, respectively, after ingestion of each dose. Thus, the highest recoveries of 4-nitrophenol occurred during the first 4 hours after exposure. Dimethyl phosphate was excreted mainly during the interval from 4 to 8 hours after exposure (Morgan et al. 1977). However, there was a low and variable recovery of alkyl phosphate metabolites from spiked urine samples (Morgan et al. 1977). Nevertheless, the available data suggest that methyl parathion metabolites are rapidly excreted in humans following oral exposure.

Urinary excretion of metabolites of methyl parathion is rapid and efficient in animals (Braeckman et al. 1983; Hollingworth et al. 1967). In mice, 70–80% of the ^{32}P activity was excreted in the urine within 72 hours after an acute exposure to radiolabeled methyl parathion (Hollingworth et al. 1967). Excretion in the feces represented, at most, 10% of the total radioactivity recovered. Dimethyl phosphate was the major metabolite in mice (Hollingworth et al. 1973). At 24 hours, urinary excretion of dimethyl phosphate was 53 and 31.9% of the activity for 3- and 17-mg/kg doses, respectively (Hollingworth et al. 1973). In rats, urinary dimethyl thiophosphate accounted for 27% of the dose of radioactivity from 2 mg/kg of methyl parathion 24 hours after oral administration. In two dogs, the cumulative radioactivity in the urine 6 days after exposure was 63 and 78% of the 3 mg/kg oral dose (Braeckman et al. 1983). Single oral (gavage) doses of 1.4–7.0 mg methyl parathion/kg, administered to rats, were followed by 24-hour excretion of 2.8–22.0 µg 4-nitrophenol/mL urine with a linear correlation (Chang et al. 1997).

The available evidence suggests that excretion of methyl parathion metabolites in humans and animals following acute oral exposure is essentially the same and occurs rapidly. Excretion occurs primarily via the urine. Methyl parathion can also be excreted in breast milk, although it has been detected only in a limited number of samples from women of central Asia, for which exposure data were not available (Lederman 1996) (see also Section 3.4.2.2). A study in rats also reported excretion of methyl parathion in the milk (Golubchikov 1991; Goncharuk et al. 1990).

3.4.4.3 Dermal Exposure

Only two studies were available that reported detection of a metabolite of methyl parathion in the urine of persons dermally exposed to methyl parathion (Ware et al. 1974, 1975). Four subjects were exposed for 5 hours to a methyl parathion formulation in a field that had been sprayed 24 hours prior to exposure (Ware et al. 1974). At 48 hours, an average of 0.5 mg 4-nitrophenol was found in the urine, but

4-nitrophenol recoveries were low and variable. In a later study using a different analytical method, an average of 1.98 mg 4-nitrophenol was measured in the urine of five men exposed for 5 hours (Ware et al. 1975). The absorption, distribution, and excretion of methyl parathion were evident from these studies. Air levels in the Ware et al. (1975) study averaged 12.6 ng/m^3, with an average respiratory dose of 75 ng for the 5-hour exposure. Dislodgeable residues on the skin just after spraying (at a level of 1 lb active ingredient/acre) ranged from 3.5 to 24 mg, and after 12 hours, they were 2.1–16 mg.

In a study of pregnant rats that were exposed to radiolabeled methyl parathion by single dermal application, half-life elimination rate constants for various tissues ranged from 0.04 to 0.07 $hour^{-1}$, highest values noted in plasma, kidneys, and fetus. Of the applied radioactivity, 14% was recovered in the urine in the first hour postapplication. By the end of the 96-hour study, 91% of the applied dose had been recovered in the urine. Fecal excretion accounted for only 3% of the administered dose (Abu-Qare et al. 2000).

3.4.4.4 Other Routes of Exposure

The elimination of methyl parathion following intravenous injection is rapid in dogs (Braeckman et al. 1980, 1983). Two dogs received 3 mg/kg ^{35}S-methyl parathion intravenously. Urinary excretion was 80–96% of the dose of radioactivity within the 6 hours following injection. Measurement of plasma concentrations of radioactivity before and after passage through the liver indicated high hepatic extraction (Braeckman et al. 1983). Thus, similar elimination data were obtained for both the intravenous and oral routes of exposure. The mean terminal half-life for elimination of a 10-mg/kg intravenous dose of methyl parathion was determined through modeling of the data to be 7.2 hours (Braeckman et al. 1980).

3.4.5 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.

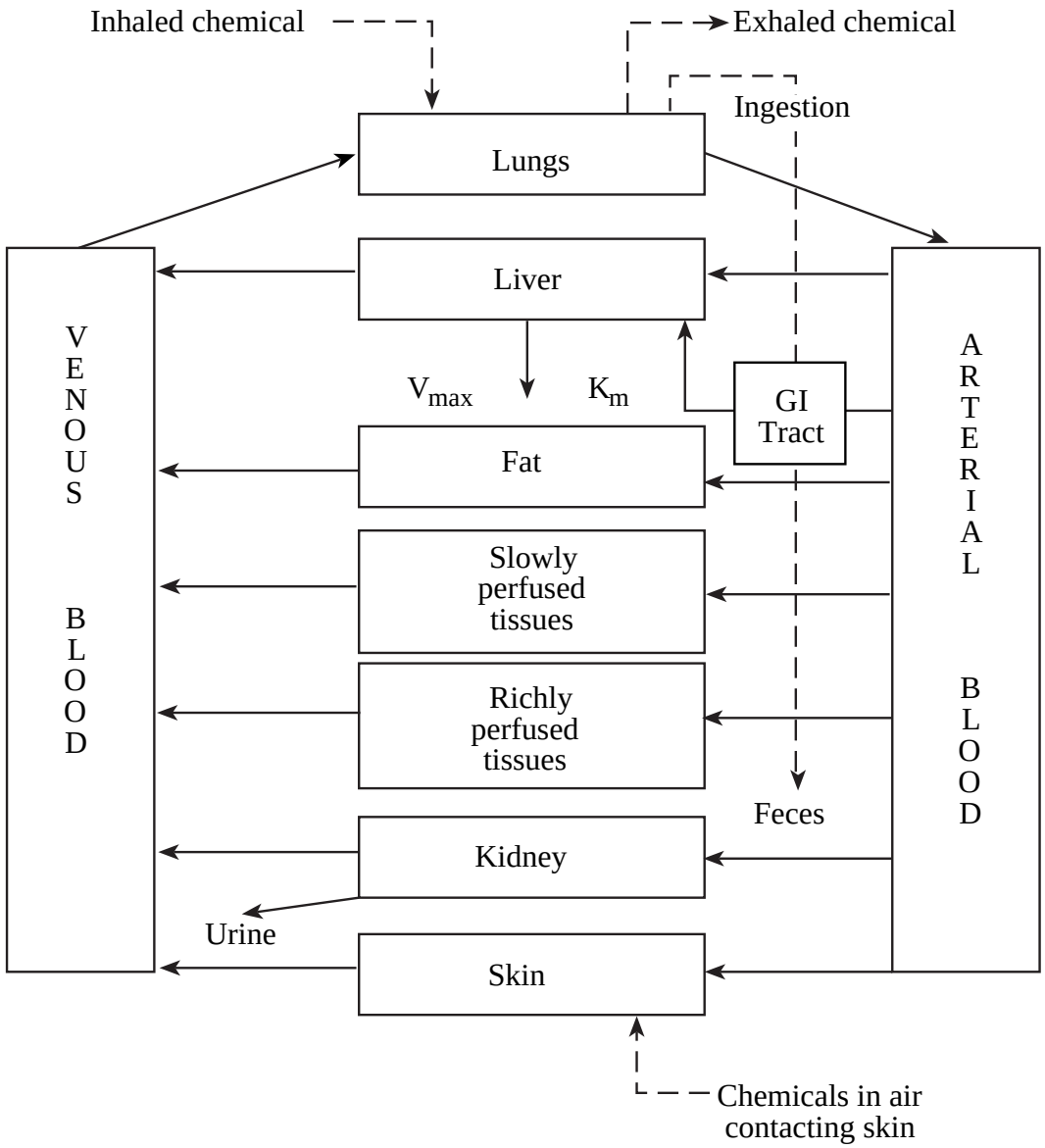
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 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 3-4 shows a conceptualized representation of a PBPK model.

Figure 3-4. 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.

No PBPK models were identified for methyl parathion.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Based on the rapid appearance of clinical signs and cholinesterase inhibition, methyl parathion appears to be readily absorbed by humans and animals following inhalation, oral, and dermal exposure. Following oral administration of methyl parathion to animals, the extent of absorption was at least 77–80% (Braeckman et al. 1983; Hollingworth et al. 1967). No studies were located regarding the extent of absorption following inhalation and dermal exposure, or the mechanism of absorption.

Data from a single study in dogs suggest that hepatic first-pass metabolism may limit systemic availability of the parent compound following oral exposure (Braeckman et al. 1983). Placental transfer of methyl parathion was demonstrated in pregnant rats 1–3 days before parturition. Thirty minutes after administration, both methyl parathion and methyl paraoxon were found in fetal brain, liver, and muscle; methyl parathion, but not methyl paraoxon, was detected in placenta and maternal liver (Ackermann and Engst 1970). Methyl parathion binds reversibly to serum albumin, but is readily distributed to the tissues (Braeckman et al. 1980, 1983).

Methyl parathion is activated by desulfuration to its toxic metabolite, methyl paraoxon, by microsomal oxidases (cytochrome P-450) (Benke and Murphy 1975; Benke et al. 1974; Hollingworth et al. 1973; Nakatsugawa et al. 1968). The specific isozyme(s) that catalyze this reaction for the phosphorothioate esters, such as parathion and methyl parathion, do not appear to have been identified. Detoxification can occur through a number of pathways, including oxidation and removal of the aryl group from the parent compound, also mediated by microsomal oxidases (P-450 isozyme not known) (Benke and Murphy 1975; Benke et al. 1974; Nakatsugawa et al. 1968). Additional detoxification pathways include glutathione-mediated dearylation of the parent compound, and hydrolysis or glutathione-mediated dealkylation or dearylation of methyl paraoxon (Benke and Murphy 1975; Benke et al. 1974). The importance of the glutathione-mediated pathways *in vivo*, however, is unclear (Chambers et al. 1994; Huang and Sultatos 1993; Zhang and Sultatos 1991). An additional inactivating mechanism may be binding to tissue and plasma constituents (Benke and Murphy 1975), including plasma cholinesterase (Parkinson 1996), making methyl parathion unavailable.

3.5.2 Mechanisms of Toxicity

Almost all systemic effects of methyl parathion are related to the action of this compound on the nervous system or are secondary to this primary action. It is therefore necessary to preface a description of the mechanisms of toxicity of methyl parathion with a brief discussion of the nervous system and neurohumoral transmitters (excerpted from Lefkowitz et al. 1996).

Neurohumoral transmitters are chemicals that facilitate the transmission of nerve impulses across nerve synapses and neuroeffector junctions. Acetylcholine is a neurohumoral transmitter that is present in the peripheral autonomic nervous system, in the somatic motor nervous system, and in some portions of the central nervous system.

The autonomic nervous system is also called the involuntary nervous system; nerve fibers innervate heart, blood vessels, glands, various visceral organs, and smooth muscles. The autonomic nervous system is further divided into the parasympathetic and sympathetic systems. Both systems are involved in regulating the internal environment of the body and act in a contrasting manner. In general, the parasympathetic system is responsible for the maintenance of normal visceral organ functions including digestion and voiding; the sympathetic system has connections to the adrenal medulla and is geared for the body's "fight or flight" mechanisms. In the autonomic system, acetylcholine is a neurohumoral transmitter for all of the first set of neurons in this system (preganglionic fibers), for all of the second set of parasympathetic fibers (postganglionic fibers), and for a few postganglionic sympathetic fibers. These are all termed cholinergic fibers.

The somatic motor nervous system or voluntary nervous system consists of nerve fibers that innervate skeletal muscle motor end-plates.

Following release of acetylcholine at a nerve synapse or at a neuromuscular junction, the transmitter is rapidly hydrolyzed (within less than a millisecond) by an enzyme called acetylcholinesterase. This enzyme is present in high concentrations in cholinergic neurons and is localized at skeletal muscle end-plates. Acetylcholinesterase is a highly efficient enzyme capable of hydrolyzing $6x10^5$ acetylcholine molecules per molecule of enzyme per minute (Taylor 1996).

Acetylcholinesterase contained in erythrocytes is identical to that found in the nervous system. Its function within erythrocytes may be to control permeability of the cell membrane, to an extent.

Functional neurological changes due to acute organophosphate exposure generally correlate with acetylcholinesterase inhibition in erythrocytes (Wills 1972).

There is a second type of cholinesterase called butyrylcholinesterase, pseudocholinesterase, or cholinesterase. This enzyme is present in some nonneural cells in the central and peripheral nervous systems as well as in plasma and serum, the liver, and other organs. Its physiologic function is not known, but is hypothesized to be the hydrolysis of esters ingested from plants (Lefkowitz et al. 1996). Plasma cholinesterases are also inhibited by organophosphate compounds through irreversible binding; this binding can act as a detoxification mechanism as it affords some protection to acetylcholinesterase in the nervous system (Parkinson 1996; Taylor 1996).

Methyl parathion and other organophosphates and their active metabolites exert their profound toxic effect by inhibiting the activity of acetylcholinesterase in the nervous system and at the motor end-plate. The active metabolite of methyl parathion, methyl paraoxon, inactivates acetylcholinesterase by phosphorylating the active site of the enzyme. The initial binding is somewhat reversible over a period of several hours, but over the following 24–48 hours, a process called “aging” occurs, resulting in the formation of a more stable covalent bond. Aging results from the removal of one of the alkyl side-chains of the phosphate group, leaving a hydroxyl group. This change prevents regeneration of the active enzyme, possibly by causing a conformational change that prevents the access of water for dephosphorylation, and represents an irreversible inhibition of the enzyme. Activity is regained only through the synthesis of new enzyme. Hydrolysis of acetylcholine is inhibited and the neurotransmitter accumulates at its site of action, producing overstimulation of cholinergic end organs, as described below (Proctor et al. 1988; Sultatos 1994; Taylor 1996).

Clinical signs and symptoms of toxicity are related to the overstimulation of muscarinic, nicotinic, and central nervous system receptors in the nervous system. Muscarinic receptors are those activated by the alkaloid drug muscarine. These receptors are under the control of the parasympathetic nervous system, and their hyperactivity results in respiratory and gastrointestinal dysfunction, incontinence, salivation, bradycardia, miosis, and sweating. Nicotinic receptors are those activated by nicotine. Hyperactivity of these receptors results in muscle fasciculations; even greater stimulation results in blockade and muscle paralysis (Lefkowitz et al. 1996; Tafuri and Roberts 1987). Hyperactivity of central nervous system receptors results in the frank neurological signs of confusion, ataxia, dizziness, incoordination, and slurred speech, which are manifestations of acute intoxication. Muscarine and nicotine are not

physiological stimulants, but rather are exogenous drugs that have been used experimentally to differentiate between the two types of receptors in the cholinergic system.

The phenomenon of tolerance is well recognized in humans and other animal species after repeated exposure by various routes to sublethal doses of organophosphates (Costa et al. 1982). Typical cholinergic signs will occur after the initial exposure to an organophosphate; signs then diminish or disappear with continued dosing at the same level. A hypothetical mechanism for tolerance is down-regulation, or decrease in the number of active muscarinic cholinergic receptors. Tolerance appears to be an adaptive response to organophosphate exposure.

The mechanisms for the observed decrease in susceptibility of rats to the lethality of methyl parathion with increasing age may be age-related changes in metabolism. The deactivating pathways appear to increase, relative to the activating pathway, with increasing age from 1 to 60 days of age, leading to the hypothesis that detoxification pathways may be more effective in adult rats than in younger ones (Benke and Murphy 1975). These conclusions are based on the correlations of *in vitro* metabolism data with LD_{50} values; additional detail is provided in Section 3.3.3.

In addition to effects mediated through glucocorticoid secretion (stress-related), a hypothetical mechanism for direct immunotoxicity of organophosphates is the inhibition of esterases and stabilization of the lysosomal membrane of lymphocytes, thus blocking release of lymphokines (Sharma and Reddy 1987).

3.5.3 Animal-to-Human Extrapolations

Rigorous within-study comparisons of the toxicokinetics and health effects of methyl parathion in humans and experimental animals are generally not available, but across-study comparisons suggest that the kinetics and effects tend to be similar across species, with the following exception. The chicken, a test animal in studies of delayed neurotoxicity, is considered to be a good indicator species for delayed neurotoxicity. Treatment of chickens with methyl parathion did not cause signs of delayed neurotoxicity (Gaines 1969). Studies in rats, however, have indicated that intermediate or intermediate-to-chronic exposure to methyl parathion may result in decrements in nerve conduction (Desi et al. 1998) and in distal axonopathy (Suba 1984). The potential for methyl parathion to cause delayed neurotoxicity, and the relevance to humans of the negative findings in chickens versus the positive findings in rats, is unclear. This effect has not been observed in humans exposed to methyl parathion.

3.6 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 1997). 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).

For methyl parathion, most of the information on health effects in humans is derived from cases of acute exposure to relatively high concentrations of the pesticide. Such reports have not addressed the issue of the potential endocrine-disrupting capacity of methyl parathion in humans. An added complication in determining whether methyl parathion has endocrine-disrupting capabilities in humans is the fact that humans are seldom exposed to a single pesticide.

Studies in experimental animals have evaluated a wide array of relevant end points and the results have been mixed. For example, methyl parathion was not toxic to male germ cells from mice administered the test material in the diet or drinking water at up to the maximum tolerated dose (not specified) (Degraeve et al. 1985; Waters et al. 1982), but a later study showed that doses between 9.4 and 75 mg methyl parathion/kg increased the percentages of abnormal sperm cells in a dose-related manner (Mathew et al. 1992). Repeated exposure of pregnant rats to an oral methyl parathion dose of 1.5 mg/kg, a dose that caused frank neurotoxicity, resulted in increased fetal resorptions (Gupta et al. 1984, 1985). Similar exposure of pregnant rats to 1 mg/kg/day of methyl parathion resulted in alterations in some behavioral end points in their offspring, evaluated at 2–6 months old (Gupta et al. 1985), suggesting that exposure *in*

utero may lead to persistent effects; however, whether this may have been caused by an endocrine-disrupting mechanism cannot be determined. Similar results had been reported earlier by Crowder et al. (1980) following gavage administration of 1 mg/kg/day to pregnant rats.

Intraperitoneal administration of a dose of 60 mg methyl parathion/kg to pregnant mice resulted in increased incidence of cleft palate in the fetuses and fetal deaths (Tanimura et al. 1967). In a more recent study, gavage administration of 1.5 mg methyl parathion/kg/day to rats on days 6–15 of gestation resulted in increased resorptions, decreased fetal body weight, and hemorrhagic spots in the brain ventricles and skin of the upper body of some of the fetuses (Kumar and Devi 1996). This dose level, however, also caused maternal toxicity expressed as cholinergic signs and depressed body weight gain.

Decreased ovarian weight gain and inhibition of compensatory ovarian hypertrophy was observed in hemi-ovariectomized rats injected intraperitoneally with methyl parathion for 15 days at 5 mg/kg/day, in comparison with hemi-ovariectomized controls (Asmathbanu and Kaliwal 1997; Dhondup and Kaliwal 1997). A decrease in the number of healthy follicles, no change in the number of atretic follicles, increase in duration of diestrus, decrease in the number of estrous cycles, and decrease in uterine weight also occurred in the methyl parathion-treated rats. Body weight gain was not decreased by methyl parathion, indicating that the effects were not due to nutritional deficiency. The effects of methyl parathion were not fully consistent with those of chlorinated pesticides that have estrogenic activity because methyl parathion did not increase follicular atresia, estrus duration, or uterine weight.

Collectively, the findings in experimental animals are insufficient to categorize methyl parathion as an endocrine-disrupting chemical.

The potential endocrine-disrupting capacity of methyl parathion in wildlife has also been examined, and results of some recent studies are summarized below.

Exposure of two species of freshwater fish to 0.106 ppb of a commercial formulation containing 50% methyl parathion increased serum levels of T3 and reduced T4 (Bhattacharya 1993). This effect was attributed to inhibition of acetylcholinesterase activity in the fish brain, but no direct evidence was presented. Similar treatment of freshwater perch for 35 days resulted in decreased release of progesterone from the ovaries (Bhattacharya and Mondal 1997). Also, treatment of freshwater perch for up to 90 days with methyl parathion induced a decrease in the gonadosomatic index (not defined) after day 15 of

exposure and in profiles of 17β-estradiol in serum and ovary that differed considerably from those in control animals over the exposure period (Choudhury et al. 1993).

Exposure of male and female Japanese quail to 3, 12, or 48 ppm methyl parathion in the diet for 6 weeks throughout the laying period resulted in reduced number of eggs laid and in increased percentage of cracked eggs at the highest exposure level (Solecki et al. 1996). The highest exposure level also resulted in decreased plasma cholinesterase, whereas brain cholinesterase was reduced at all exposure levels. Neither fertility nor hatchability were affected by treatment. Oral treatment of wild passerine birds (*Lonchura malabarica*) with up to 200 µg methyl parathion/kg resulted in a significant reduction in testes weight at $100 µg/kg after 10 days of treatment (Maitra and Sarkar 1996). However, a single dose of 50 µg/kg induced a significant decrease in the number of tubules containing healthy germ cells; the frequency and severity of this effect was dose-related and related to exposure duration. The authors also reported that effect on tubular germ cells was negatively correlated with acetylcholinesterase activity in the testes and brain and suggested that cholinergic activity may play a role in the influence of methyl parathion on gametogenic activities in the testes. Alternatively, they noted that brain cholinergic activity may also play a role through regulation of gonadotrophic secretion.

In addition to *in vivo* tests, *in vitro* assays have been developed to test for hormone-mimicking properties of chemicals. These tests include cell proliferation assays and gene expression assays in mammalian cells and yeast. Although easy to conduct, these assays can yield both false negatives and false positives; for this reason, it is preferable to perform both *in vivo* and *in vitro* assays before classifying a chemical as to its endocrine-disrupting capacity. Limited information exists in this regard for methyl parathion. Methyl parathion exhibited very weak estrogenic properties (>10,000 times less potent than 17β-estradiol) in a yeast system expressing rainbow trout estrogen receptor (Petit et al. 1997). However, methyl parathion had an estrogenic potency similar to 17β-estradiol in a test in trout hepatocyte aggregate cultures that express the estrogen receptor (Petit et al. 1997). The structurally-related organophosphate pesticide, parathion, did not show estrogenic properties in breast cancer estrogen-sensitive MCF-7 cells (Soto et al. 1995).

In summary, while there is information on effects of methyl parathion that could be considered as endocrine-mediated, the less than optimal quality of the many of the studies do not allow for firm conclusions. Further research is needed to clarify whether methyl parathion may act as an endocrine disruptor.

3.7 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 6.6 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 while 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).

Present information indicates a potential for age-related differences in susceptibility to methyl parathion. However, data are limited in both human and animal studies.

Acute exposure (via inhalation, dermal, and/or oral exposure routes) to methyl parathion has resulted in typical symptoms of organophosphate poisoning including depressed plasma and erythrocyte cholinesterase levels, altered function of nervous, cardiac, pulmonary, and gastrointestinal systems, and death in adults (Fazekas 1971; Fazekas and Rengei 1964) and children (Dean et al. 1984), indicating similarity in targets of toxicity from exposure to methyl parathion (see Section 3.5 for a more complete description of organophosphate poisoning). Toxicity in the nervous system is elicited by inhibition of the enzyme, acetylcholinesterase, which helps to control the level of the neurotransmitter acetylcholine. Lower levels of acetylcholinesterase result in effectively higher concentrations of acetylcholine and hyperactivity within the nervous system.

Acetylcholine, acetylcholinesterase, and butyrylcholinesterase are involved in the development of the nervous system (Brimijoin and Koeninsberger 1999; Layer 1990; Layer and Willbold 1994); some of this development is not complete until adulthood. Therefore, toxic chemicals acting on these substances could cause deleterious developmental effects in addition to the typical physiological effects already discussed.

Limited information regarding potential for age-related differences in susceptibility to methyl parathion in humans was reported by Dean et al. (1984). Seven children (ranging in age from 2 to 11 years) and three adults were exposed to unknown concentrations of methyl parathion sprayed illegally inside a house at a concentration of 4% (>3 times the recommended concentration for field applications). The children

exhibited typical signs of organophosphate poisoning; two of them (4 and 11 years of age) died of respiratory arrest. Although the adults did not exhibit typical overt signs of methyl parathion poisoning, urinary levels of a methyl parathion metabolite (4-nitrophenol) were as high in the adults as in some of the children exhibiting toxic effects. The potential for age-related susceptibility could not be clearly assessed since critical information on individual exposure levels and routes was lacking.

The only other information regarding the potential for age-related differences in susceptibility to methyl parathion came from a study by Garcia-Lopez and Monteoliva (1988). The investigators showed increasing mean erythrocyte acetylcholinesterase activity levels with increasing age range, starting at birth (in 10-year increments and >60 years of age) in both males and females. However, it is not known whether increased erythrocyte acetylcholinesterase activity indicates a decreased susceptibility to methyl parathion toxicity.

Age-related differences in LD_{50} values for methyl parathion administered intraperitoneally have been shown in rats, with perinates being most susceptible and LD_{50} values increasing with age through adults (Benke and Murphy 1975; Kimmerle and Lorke 1968). The greatest change in LD_{50} values occurred in pups between 1 and 12–13 days old (Benke and Murphy 1975). While no significant age-related differences were noted in the *in vitro* inhibition of cholinesterase in brain homogenates treated with methyl paraoxon, *in vitro* metabolic studies of methyl parathion provide some evidence that age-related variation in a number of metabolic reactions might account, in part, for observed age-related changes in lethality. This age-related evidence includes positive correlations between changes in LD_{50} values for methyl parathion and ratios of oxidative deactivation (reaction 2 in Figure 3-3) to oxidative activation (reaction 1) of methyl parathion, as well as increases in hydrolysis (reaction 3), glutathion-dependent dealkylation and dearylation (reactions 5 and 7), and tissue binding of methyl paraoxon (Benke and Murphy 1975). The decreased susceptibility to methyl parathion toxicity (i.e., increased LD_{50} values) with increasing age was attributed to more effective detoxification in older rats relative to younger ones (Benke and Murphy 1975). However, *in vivo* studies have yet to confirm this hypothesis, and it is not known whether age-related differences in detoxification rates would play a role in low-level acute or chronic exposure scenarios.

Pope et al. (1991) found that 7-day-old Sprague-Dawley rat pups were approximately twice as sensitive as 80–100-day-old adults to single subcutaneous doses of methyl parathion; the highest nonlethal dose 7.8 mg/kg for the neonates and 18.0 mg/kg for adults. Initially, both neonates and adults exhibited similarly reduced brain acetylcholinesterase activity levels (approximately 10% that of controls);

however, recovery of cholinesterase activity was more rapid in neonates (approximately 75% at 4 days posttreatment compared to only 30% in adults). In a subsequent study, Pope and Chakraborti (1992) showed that these age-related effects also occurred in a dose-related manner. Using daily subcutaneous dosing for 14 days, Liu et al. (1999) found that brain acetylcholinesterase activity was inhibited to a significantly greater extent in neonatal than in adult rats during dosing with 1.5 mg/kg/day, but that 8 days after termination of exposure, there was little or no difference. The difference was diminished at a higher dose of 3 mg/kg/day, and recovery of activity was higher in the neonates after 8 days post-exposure. Two other animal studies reported age-related responses to methyl parathion exposure by the oral route. Kumar and Desiraju (1992) found no statistically significant difference in the magnitude of brain acetylcholinesterase inhibition in 15-day-old Wistar rat pups and 90-day-old adults (approximately 47 and 60%, respectively) following single oral (gavage) doses of 1 mg/kg.

Placental transfer of methyl parathion was demonstrated in pregnant rats after oral administration of 11.1 mg methyl parathion/kg body weight (Ackermann and Engst 1970). Following sacrifice 30 minutes posttreatment, maternal liver and placenta were found to contain measurable amounts of methyl parathion, but not methyl paraoxon. Fetal brain, liver, and muscle tissues contained methyl parathion concentrations up to approximately 2.5 times that of the maternal liver. Similarly, placental transfer was demonstrated in pregnant rats following dermal application of 10 mg methyl parathion/kg (Abu-Qare et al. 2000). By 4 hours postadministration, the highest concentration of methyl parathion was found in fetal tissue; the concentration in placental tissue was about as high as that of the maternal liver. Fish (1966) gave supporting evidence for placental transfer of methyl parathion and/or its toxic metabolites by demonstrating that brain cholinesterase activity was reduced in fetal rats following intraperitoneal injections of the pregnant dams with maternally-toxic doses of methyl parathion. Methyl parathion was found in breast milk in a limited number of samples from women of central Asia, for which exposure data were not available (Lederman 1996) (see also Section 3.4.2.2). This indicates that methyl parathion might be transferred from contaminated mother to nursing infant. No information was locating regarding the presence of methyl parathion metabolites in breast milk. A study of a mixture of pesticides (methyl parathion, lindane, and permethrin) in rats reported that following oral exposure of the dams on lactation days 1–14, methyl parathion was present in higher concentrations in their milk and in the pups' blood than in the dams' blood (Golubchikov 1991; Goncharuk et al. 1990). Confidence in this study is low because descriptions of the methods and results were cursory.

It is not presently known what phase I enzymes metabolize methyl parathion, and consequently, whether metabolism differs between children and human adults. There is some suggestive evidence for age-related differences in metabolism of methyl parathion in rats (Benke and Murphy 1975).

Tanimura et al. (1967) reported increased incidences of cleft palate and mortality in fetuses of pregnant mice injected intraperitoneally with 60 mg methyl parathion/kg. Significantly reduced maternal and fetal brain acetylcholinesterase activity, increased resorptions (Gupta et al. 1985), and dose-related reductions in net maternal and fetal protein synthesis (Gupta et al. 1984) were noted following oral exposure of pregnant rats to methyl parathion during gestation. Crowder et al. (1980) reported increased mortality in rat pups (relative to controls) following oral administration of methyl parathion to pregnant dams during gestation and a significant difference in maze transfer tests between treatment and control groups. Kumar and Devi (1996) also reported treatment-related maternal and fetal effects in rats following oral administration of methyl parathion to dams during gestation. However, there were no reports of age-related differences in susceptibility to methyl parathion in any of these studies.

Dose-related changes on electrocorticograms and on nerve conduction velocity and refractory period were reported in rats that were exposed to methyl parathion via treatment of the dams during gestation and lactation, and then orally at dose levels of 0.22, 0.44, or 0.88 mg/kg/day for 8 more weeks of postnatal development to the age of 12 weeks (Desi et al. 1998). These effects were not seen in 12-week-old rats following exposure only during gestation and lactation or gestation alone. No overt toxic signs were seen in dams or offspring.

3.8 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 methyl parathion are discussed in Section 3.8.1.

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 methyl parathion are discussed in Section 3.8.2.

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 3.10 Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Methyl Parathion

The most specific biomarker of exposure to methyl parathion is the presence of the compound in serum or tissue. This is an especially good biomarker for detection shortly after acute exposure. For example, methyl parathion levels were detected in the sera of five men who were exposed for 5 hours in a cotton field 12 hours after it was sprayed with methyl parathion. The route of exposure was dermal, through unprotected hands. Serum levels averaged 156 ppb after 3 hours of the 5-hour exposure, and averaged 101.4 and 2.4 ppb at 7 and 24 hours postexposure, respectively (Ware et al. 1975).

These results are supported by studies in animals in which methyl parathion was detected 30–155 minutes after exposure (oral, dermal, inhalation, or intravenous routes) in plasma and liver (Abu-Qare et al. 2000; EPA 1978e). Due to extensive and rapid metabolism of methyl parathion (see Section 3.3), measurable levels are not expected to persist in tissue or serum for prolonged periods after exposure.

Urine of exposed humans can also be monitored for two metabolites of methyl parathion: 4-nitrophenol (measured after hydrolysis of the glucuronide, Section 3.3.4) and dimethyl phosphate. After ingestion of 2 or 4 mg of methyl parathion, maximum urinary excretion occurred as follows: 4-nitrophenol within 4 hours, and dimethyl phosphate between 4 and 8 hours. Metabolites were not detected in urine on the second day after exposure (Morgan et al. 1977). Metabolites, such as 4-nitrophenol, have also been detected in stomach contents, urine, and tissues of humans committing suicide by ingestion of methyl parathion (Fazekas 1971). These metabolites are not, however, specific for methyl parathion. The metabolite 4-nitrophenol can also occur as a breakdown product of other organophosphate insecticides such as parathion as well as some nonorganophosphate compounds, while alkylphosphates are metabolic end-products of most organophosphates (Davies and Peterson 1997; Morgan et al. 1977).

Urinary 4-nitrophenol was detected in intoxicated children and clinically normal adults in a household where there had been exposure to methyl parathion (Dean et al. 1984).

Associations between urinary 4-nitrophenol and indoor residential air and surface-wipe concentrations of methyl parathion have been studied in 142 residents of 64 contaminated homes in Lorain, Ohio (Esteban et al. 1996). The homes were contaminated through illegal spraying. A mathematic model was developed to evaluate the association between residential contamination and urinary 4-nitrophenol. There were significant positive correlations between air concentration and urinary 4-nitrophenol, and between maximum surface-wipe concentrations and urinary 4-nitrophenol. The final model includes the following variables: number of days between spraying and sample collection, air and maximum surface wipe concentration, and age, and could be used to predict urinary 4-nitrophenol.

3.8.2 Biomarkers Used to Characterize Effects Caused by Methyl Parathion

Diagnosis of organophosphate poisoning (including methyl parathion) can be confirmed by evaluation of serum (plasma) cholinesterase and erythrocyte cholinesterase. However, cholinesterase inhibition is not specific for organophosphates. For example, carbamate insecticides also result in cholinesterase inhibition, which is usually transitory. Erythrocyte cholinesterase measurement is a specific test for

acetylcholinesterase inhibition since it is found in both the peripheral and central nervous systems. However, measurement is complicated by the fact that normal erythrocyte cholinesterase values encompass a broad range in the human population (Midtling et al. 1985; Tafuri and Roberts 1987). Serum cholinesterase (pseudocholinesterase) is a more sensitive but less specific indicator of organophosphate toxicity since the levels may also be suppressed due to genetic factors and to a variety of conditions and diseases (Henry 1984; Tafuri and Roberts 1987). Acetylcholinesterase activity recovers as a result of the synthesis of new enzyme and recovery generally occurs at a rate of approximately 1% per day. However, the symptoms of methyl parathion poisoning usually resolve more rapidly. Therefore, even if they are symptom-free, persons poisoned by methyl parathion may have lowered cholinesterase levels for a month after exposure and should avoid re-exposure for several weeks (Proctor et al. 1988). Also, normal values may have interlaboratory variation (NIOSH 1976). Several field tests for measuring erythrocyte acetylcholinesterase and plasma cholinesterase are available (Wills 1972). Baseline data are often collected for workers, but these data would not be available for environmentally exposed people. Sequential determinations of cholinesterase levels from individuals probably exposed to methyl parathion could be an alternative method of determining cholinesterase inhibition (Midtling et al. 1985). In interpreting results, it should be noted that there are both age- and gender-related differences in normal erythrocyte and plasma cholinesterase levels in humans (Garcia-Lopez and Monteoliva 1988; Wills 1972). See Sections 3.7 and 3.10 for additional information on these age- and gender-related differences.

A classification of organophosphate poisoning has been proposed by Tafuri and Roberts (1987) modified from Namba et al. (1971). Clinical signs and symptoms of intoxication may occur when serum cholinesterase levels drop to below 50% of the normal value. Mild poisoning, with the patient still ambulatory, may occur when serum cholinesterase levels are 20–50% of normal; moderate poisoning with inability to walk with levels 10–20% of normal; and severe poisoning with respiratory distress and unconsciousness with serum cholinesterase levels <10% of normal.

Following exposure of humans to organophosphates, but not specifically methyl parathion, restoration of plasma cholinesterase occurs more rapidly than does restoration of erythrocyte cholinesterase (Grob et al. 1950; Midtling et al. 1985). These findings are supported by studies of methyl parathion in animals. Erythrocyte cholinesterase levels are representative of acetylcholinesterase levels in the nervous system, and, therefore, may be a more accurate biomarker of the neurological effects of chronic low level exposure of humans to methyl parathion (Midtling et al. 1985; NIOSH 1976).

3.9 INTERACTIONS WITH OTHER CHEMICALS

Emergency therapy of acute organophosphate (including methyl parathion) intoxication in humans and other mammals relies on the antagonistic interactions of several drugs. Atropine serves as a potent antidote by blocking the action of acetylcholine at muscarinic nerve receptors and, therefore, lessens clinical signs related to parasympathetic stimulation caused by the inactivation of acetylcholinesterase by methyl parathion. 2-Pyridine aldoxime methiodide (2-PAM) reverses the effect of cholinergic nicotinic stimulation such as at the motor nerve junctions with the end-plates of skeletal muscle fibers. This treatment ameliorates signs and symptoms of skeletal muscle fasciculation, muscle weakness, and life-threatening paralysis of respiratory muscles. 2-PAM is able to reactivate phosphorylated cholinesterase if the drug is administered within 24–36 hours of acute methyl parathion intoxication. After that time, irreversible changes in the phosphorylated enzyme occur, and 2-PAM is ineffective as an antidote (Tafuri and Roberts 1987).

Compounds that affect activities of hepatic microsomal enzymes can antagonize the effects of methyl parathion, presumably by decreasing metabolism of methyl parathion to methyl paraoxon or enhancing degradation to relatively nontoxic metabolites. For example, pretreatment with phenobarbital protected rats from methyl parathion's cholinergic effects (Murphy 1980) and reduced inhibition of acetyl-cholinesterase activity in the rat brain (Tvede et al. 1989). Phenobarbital pretreatment prevented lethality from methyl parathion in mice compared to saline-pretreated controls (Sultatos 1987). Pretreatment of rats with two other pesticides, chlordecone or mirex, also reduced inhibition of brain acetylcholinesterase activity in rats dosed with methyl parathion (2.5 mg/kg intraperitoneally), while pretreatment with the herbicide linuron decreased acetylcholine brain levels below those found with methyl parathion treatment alone (Tvede et al. 1989).

Cimetidine, an H_2 antagonist used therapeutically in patients with ulcers, inhibits activity of hepatic microsomal enzymes. When rats or mice were pretreated with cimetidine, dose-related lethality of methyl parathion was reduced, and cholinergic signs of toxicity were delayed. Simultaneous administration with methyl parathion did not reduce toxicity (Joshi and Thornburg 1986).

Piperonyl butoxide, a common potentiator of insecticide effects that inhibits microsomal enzymes, antagonized the toxic effects of methyl parathion in mice (Mirer et al. 1977).

Gentamicin is a broad spectrum aminoglycoside antibiotic, and rifamycin is an antituberculosis drug. Pretreatment of rats with these agents protected them against toxic effects of a single oral dose of methyl parathion. Plasma cholinesterase and liver carboxylesterase levels were higher in pretreated than untreated rats challenged with methyl parathion. Pretreated rats had significantly decreased methyl paraoxon levels in liver and skeletal muscles while 4-nitrophenol levels were increased in the urine, indicative of enhanced detoxification (Youssef et al. 1987).

Acetaminophen, which depletes hepatic glutathione, does not potentiate the toxicity of methyl parathion in mice. A possible mechanism of action may be competition between acetaminophen and methyl parathion for mixed function oxidases and subsequent prevention of activation of methyl parathion to methyl paraoxon (Costa and Murphy 1984). Diethyl maleate, an agent that depletes cytosolic glutathione and is not an enzyme inducer, potentiates toxicity of methyl parathion in mice (Mirer et al. 1977).

Permethrin, a pyrethrin pesticide, decreased the inhibition of brain cholinesterase activity by methyl parathion, but methyl parathion decreased the LD_{50} of permethrin when the two pesticides were simultaneously administered to rats (Ortiz et al. 1995). The potentiation of permethrin lethality may be due to the inhibition by methyl parathion of carboxylesterase, which metabolizes permethrin.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to methyl parathion than will most persons exposed to the same level of methyl parathion 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 methyl parathion, or compromised function of organs affected by methyl parathion. Populations who are at greater risk due to their unusually high exposure to methyl parathion are discussed in Section 6.7 Populations With Potentially High Exposures.

Unusually susceptible populations are those groups of individuals who respond more quickly or at lower exposure levels than the general population to the toxic effects of methyl parathion. These responses may be genetic in origin or may be due to differences in development or life style factors such as nutrition or behavior, or due to preexisting disease states.

People who should not work with organophosphate insecticides are those with organic central nervous system disease, mental disorders, epilepsy, pronounced endocrine disorders, respiratory conditions, cardiovascular diseases, circulatory disorders, gastroenteric diseases, liver or kidney disease, and chronic conjunctivitis and keratitis (Medved and Kagan 1983).

Individuals with hereditary low plasma cholinesterase levels (Kalow 1956; Lehman and Ryan 1956) and those with paroxysmal nocturnal hemoglobinuria, which is related to abnormally low levels of erythrocyte acetylcholinesterase (Auditore and Hartmann 1959), would have increased susceptibility to the effects of anticholinesterase agents such as methyl parathion. Repeated measurements of plasma cholinesterase activity (in the absence of organophosphate exposure) can be used to identify individuals with genetically determined low plasma cholinesterase.

Women have exhibited significantly decreased plasma cholinesterase levels (De Peyster et al. 1994; Evans and Wroe 1980; Evans et al. 1988; Howard et al. 1978; Sanz et al. 1991; Venkataraman et al. 1990) and significantly increased erythrocyte acetylcholinesterase levels (De Peyster et al. 1994; Sanz et al. 1991; Venkataraman et al. 1990) during pregnancy. It is not known whether these differences might make pregnant women more susceptible to methyl parathion toxicity.

Several studies in animals suggest that age may affect susceptibility to methyl parathion toxicity, and that children may be more susceptible than adults, but the data are limited. (See Section 3.7 for more information on Children's susceptibility.) A study in humans showed that mean erythrocyte acetyl-cholinesterase activity levels increase with increasing age from birth through old age in both sexes (Garcia-Lopez ad Monteoliva 1988), but it is not known whether increased erythrocyte acetyl-cholinesterase activity indicates decreased susceptibility to methyl parathion.

Male rodents have been shown to be more susceptible to acute toxic effects of methyl parathion than females (EPA 1978e; Murphy and Dubois 1958).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to methyl parathion. 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 methyl parathion. 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 methyl parathion:

Aaron CK, Howland, MA. 1998. Insecticides: Organophosphates and carbamates. In: Goldfrank LR, Flomenbaum NE, Lewin NA, et al., eds. Goldfrank's toxicologic emergencies. Stamford, CT: Appleton & Lange, 1429–1449.

Bronstein AC, Currance PL, eds. 1988. Emergency care for hazardous materials exposure. St. Louis, MO: CV Mosby Company, 66, 199–200.

Ellenhorn MJ. 1997. Pesticides: Insecticides. In: Ellenhorn's medical toxicology: Diagnosis and treatment of human poisoning. Baltimore, MD: Williams & Wilkins, 1614–1631.

EPA. 1989b. Recognition and management of pesticide poisonings. 4th ed. Washington, DC: U.S. Environmental Protection Agency. Health Effects Division. Office of Pesticide Programs. EPA 540/9-88-001.

3.11.1 Reducing Peak Absorption Following Exposure

Procedures that have been used to reduce absorption of methyl parathion include the following. In inhalation and dermal exposures, the exposed person is first removed from the source of exposure. Dermal absorption is then reduced by washing the skin and hair with mild soap or detergent and copious amounts of water. If immediately available, a mild hypochlorite (bleach) solution can be used on the skin (*not* in the eyes); the chlorine radical deactivates organophosphate agents. Care is taken to avoid abrading the skin as methyl parathion may be more rapidly absorbed through cuts, cracks, or abrasions in the skin (Aaron and Howland 1998). Ocular absorption is limited by irrigating the eyes with copious amounts of normal saline or lactated Ringer's solution, or, if these solutions are not available, water (Aaron and Howland 1998; Stutz and Janusz 1988). After acute oral exposures to high doses, absorption from the gastrointestinal tract is limited by gastric lavage followed by administration of activated charcoal to absorb residual methyl parathion present in the gut. Emesis with ipecac has been discouraged because coma or seizures may develop rapidly in acute high-dose situations (Aaron and Howland 1998). In low-dose situations, where swallowing is not impaired and a good gag reflex and no drooling exist, absorption of methyl parathion from the gastrointestinal tract may be limited by drinking water to dilute the contents of the gastrointestinal tract (Bronstein and Currance 1988), but this procedure will expose a larger area of absorptive surface to the toxicant.

3.11.2 Reducing Body Burden

No information was located regarding methods for reducing body burden of methyl parathion.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Methyl parathion produces its toxic effects by inhibiting acetylcholinesterase. This results in excess acetylcholine at the synapses and neuroeffector junctions. Treatment of methyl parathion poisoning is directed toward reducing the effects of the excess acetylcholine and reactivating acetylcholinesterase. Atropine may be given to block muscarinic cholinergic receptors and limit the action of acetylcholine at this class of receptors. In cases of moderately severe poisoning, a state of atropinization (tachycardia, flushing, dry mouth, dilated pupils) is maintained for extended periods (Aaron and Howland 1998; Ellenhorn 1997; Proctor et al. 1988). Pralidoxime (2-PAM) acts to reactivate acetylcholinesterase and is given in conjunction with atropine therapy. It is most effective if administered shortly after exposure to methyl parathion because the inhibited acetylcholinesterase molecule becomes resistant to reactivation (aging) within several hours (24–36 hours). Therapy with 2-PAM is continued for at least 18 hours (Aaron and Howland 1998; Ellenhorn 1997; EPA 1989b). However, prophylactic administration of atropine and/or 2-PAM prior to organophosphate exposure is not recommended (EPA 1989b). The intermediate syndrome, which has been reported for some organophosphate pesticides, including a mixture of parathion and methyl parathion, may cause respiratory insufficiency or arrest 1–4 days after resolution of the acute cholinergic crisis. Therefore, patients exposed to organophosphates associated with this syndrome are observed for a more prolonged period of time, and may be continued on 2-PAM therapy after resolution of the cholinergic crisis (Aaron and Howland 1998).

Following inhibition by methyl parathion, acetylcholinesterase activity recovers as a result of the synthesis of new enzyme, generally at a rate of approximately 1% per day. However, the symptoms of methyl parathion poisoning usually resolve much more rapidly. Therefore, even though they are symptom-free, persons poisoned by methyl parathion may be hypersusceptible to its effects and should avoid reexposure for several weeks (Aaron and Howland 1998; Proctor et al. 1988).

3.12 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 methyl parathion 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 methyl parathion.

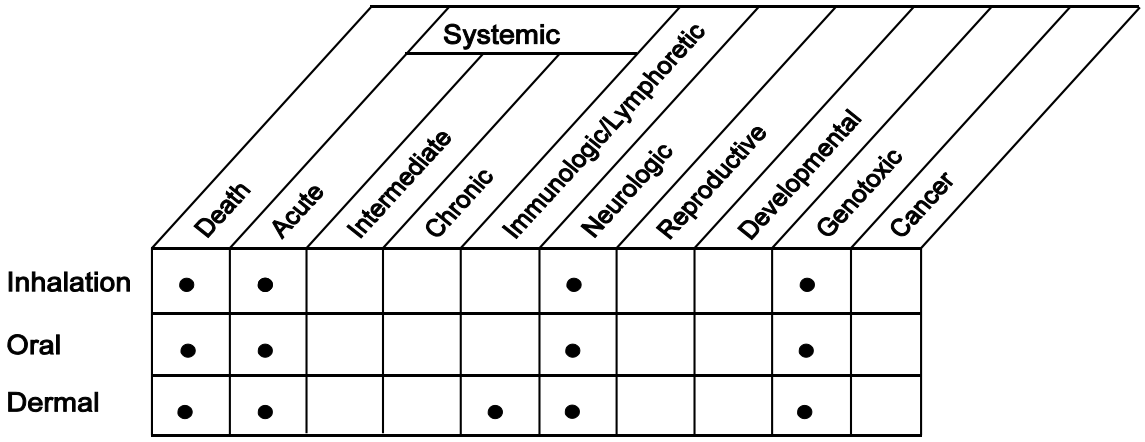
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean 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.

3.12.1 Existing Information on Health Effects of Methyl Parathion

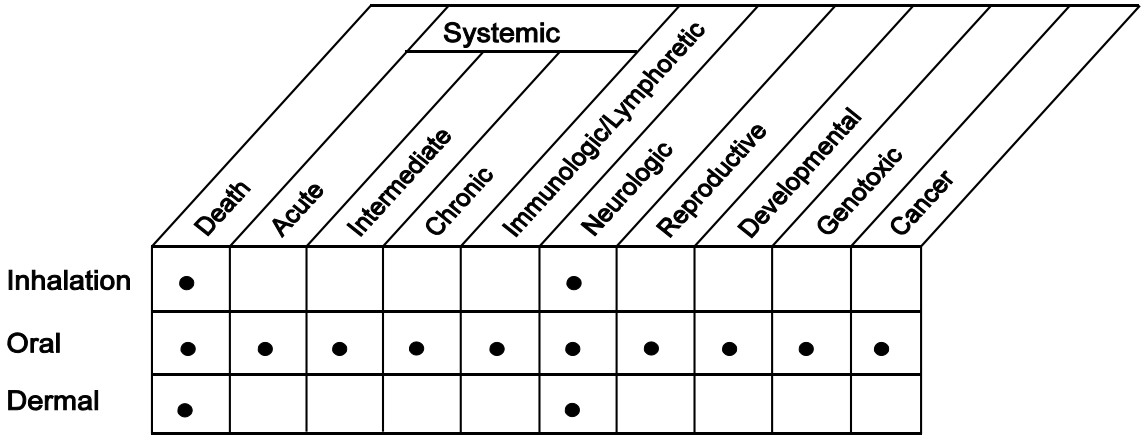
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to methyl parathion are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of methyl parathion. Each dot in the figure indicates 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.

Figure 3-5 graphically depicts the information that currently exists on the health effects of methyl parathion in humans and animals by various routes of exposure. The available literature reviewed concerning the health effects of methyl parathion in humans described case reports of longer-term studies of pesticide workers and case reports of accidental or intentional ingestion of methyl parathion. The occupational exposure is believed to be via the dermal and inhalation routes. The information on human exposure is limited in that the possibility of concurrent exposure to other pesticides or other toxic substances cannot be quantified.

Figure 3-5. Existing Information on Health Effects of Methyl Parathion



Human



Animal

● Existing Studies

The database for the health effects of methyl parathion after ingestion in experimental animals is substantial. However, as can be seen in Figure 3-5, only limited information is available on the effects of inhalation and dermal exposure to methyl parathion in animals. Furthermore, the health effects such as death and neurotoxicity resulting from acute exposure in animals are more fully studied than systemic and immunotoxic effects associated with acute exposure.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Information is available regarding acute-duration exposure in humans and animals following exposure by all three routes. However, the studies in humans via the inhalation and dermal routes involved combined exposure by both routes (Dean et al. 1984; Fazekas 1971). Acute ingestion of high doses and combined exposure to methyl parathion via inhalation and dermal routes result primarily in neurological and systemic effects in humans (Dean et al. 1984; Fazekas 1971; Fazekas and Rengei 1964). However, exposure levels in these studies were not quantified. An experimental study in humans at very low oral doses resulted in no neurological effects, but involved only two subjects, and no concurrent controls (Rodnitzky et al. 1978). The target of toxicity in humans and animals following acute, high-level exposure by any route is the nervous system (Dean et al. 1984; EPA 1978e; Miyamoto et al. 1963b; Yamamoto et al. 1982; Youssef et al. 1987). The observed effects on the liver (Fazekas 1971; Fazekas and Rengei 1964; Sonnenschein et al. 1989a, 1989b) and respiratory (EPA 1978e; Fazekas 1971) systems may be primary or secondary effects of methyl parathion toxicity following acute oral exposure in experimental animals. The observed effects have also been seen in humans from oral exposure and from combined exposure by the inhalation and dermal routes (Fazekas 1971; Fazekas and Rengei 1964). For the oral route, the highest NOAEL below a LOAEL was 0.88 mg/kg/day for developmental effects in rats (Desi et al. 1998), and this dose level was too close to a serious LOAEL of 1 mg/kg/day for neurodevelopmental effects in rats (Crowder et al. 1980) to be used for MRL derivation. Additional acute oral studies that could provide dose-response information at low exposure levels are needed. Only qualitative human data (exposure level and duration not quantified) and animal LC_{50} data are available for the inhalation route of exposure (Dean et al. 1984; Fazekas 1971; Kimmerle and Lorke 1968). No dose-response data are available. Data on neurological effects in humans or animals are not sufficient to derive an acute inhalation MRL (Dean et al. 1984; EPA 1978e). Therefore additional inhalation studies are needed. The available toxicokinetic data are not adequate to predict the behavior of methyl parathion across the routes of exposure. The limited toxicity information available indicates that similar effects are observed (i.e., death, neurotoxicity) in both animals (EPA 1978e; Miyamoto et al. 1963b; Nemec et al. 1968; Yamamoto et al. 1982; Youssef et al. 1987) and humans (Dean et al. 1984;

Fazekas 1971) exposed by various routes. Because of a lack of toxicokinetic data, it cannot be assumed that the end points of methyl parathion toxicity would be quantitatively similar across all routes of exposure. The acute effects of dermal exposures to methyl parathion are not well characterized in humans or animals. Therefore, additional dermal studies are needed.

Intermediate-Duration. No information is available on the toxicity of methyl parathion to humans following intermediate-duration exposure by any route. In an oral study in humans, 30 mg of methyl parathion administered to adult males daily for 30 days depressed erythrocyte cholinesterase levels to 37% of preexposure values; this abstract did not indicate whether toxicity was produced (Rider et al. 1971). Information is available regarding intermediate-duration exposure in animals following oral exposure; toxicity in animals is manifested by neurological (Daly 1989; Desi et al. 1998; Williams et al. 1959), gastrointestinal (NCI 1979), developmental (Gupta et al. 1985), and immunological (Shtenberg and Dzhunusova 1968; Street and Sharma 1975) effects. An intermediate-duration gavage study of methyl parathion in rats identified hematological effects of anemia (decreased erythrocyte count and hematocrit) and slight leukocytosis with neutropenia and lymphocytosis (Galal et al. 1977). However, this study had severe limitations (i.e., a dosing design which did not allow establishing effect levels) that precluded its use. These limitations included increases in dose every 4 days, lack of controls, abnormal before-treatment values, irregularities in calculations, and disparities between the text and tables. A more reliable intermediate-duration gavage study in rats found no change in leukocyte counts or differential counts (Crittenden et al. 1998). Nevertheless, because erythrocyte cholinesterase has an action of controlling erythrocyte permeability (Wills 1972), experimental data on the hematological effects of intermediate-duration exposure to methyl parathion are needed. The oral exposure data in animals from the Desi et al. (1998) study are sufficient to derive an intermediate oral MRL based on adverse neurological effects. Additional studies examining the dose-response and critical periods for neurobehavioral developmental effects of intermediate-duration oral exposure to methyl parathion are needed. Since no data are available for the inhalation route of exposure, an intermediate inhalation MRL could not be derived. The available toxicity data are not adequate to predict the behavior of methyl parathion across routes of exposure. The limited toxicity information available indicates that similar effects are observed (i.e., neurotoxic) in animals following oral, inhalation, or dermal exposure. However, it cannot be assumed that the end points of methyl parathion toxicity are quantitatively similar across all routes of exposure, and, therefore, it may not be possible to predict the levels that cause these effects by all routes of exposure. The dermal and inhalation studies of intermediate duration are needed to identify more accurately the end points of toxicity and the levels at which these effects are observed.

Chronic-Duration Exposure and Cancer. No information is available on the toxicity of methyl parathion in humans following chronic-duration exposure by any route. The oral exposure data in animals from the Suba (1984) study are sufficient to derive a chronic oral MRL based on adverse hematological effects (Suba 1984). No chronic-duration exposure data are available for the inhalation or dermal routes of exposure. Therefore, no MRL for a chronic exposure duration could be derived for the inhalation route. No data regarding potential hematological effects of inhalation or dermal exposure are available for any duration. Because other effects of methyl parathion, such as neurological effects, are seen for all three routes of exposure, hematological effects also may occur following inhalation or dermal exposure; additional testing is needed. The toxicity information available for acute-duration exposures indicate that similar effects are observed in the central nervous system from oral, inhalation, and dermal exposures. Neurological effects were observed in chronic oral exposure (Suba 1984). Additional data are needed to determine whether chronic inhalation exposures by the dermal and inhalation routes also affect the nervous system. Additional studies are needed to identify end points, in addition to the hematological and nervous systems, that are affected by chronic exposures via each of these routes, and the levels at which these effects would be observed.

No reports of cancer in humans associated with exposure to methyl parathion by any route have been found. The carcinogenicity of methyl parathion has been studied in two chronic oral bioassays using rats (NCI 1979; Suba 1984) and mice (NCI 1979). The available data in experimental animals are negative. However, limitations associated with the study by NCI (i.e., a small control group, dose adjustments during the study, high mortality in high-dose female rats, and lack of cholinesterase measurements, hematology, or clinical chemistry) render this study inappropriate for use in drawing conclusions regarding the carcinogenicity of methyl parathion.

EPA (1988a) has discussed the results of another carcinogenicity bioassay on methyl parathion in rats. Results of this study have not been presented in a peer-reviewed scientific journal and are not available to the public.

Genotoxicity. No reliable data in humans exist to indicate whether methyl parathion may act by a genotoxic mechanism. One study reported a temporary but significant increase in chromatid breaks and stable chromosomal aberrations in two subjects after ingestion of methyl parathion (Van Bao et al. 1974), but another study reported no significant differences in five subjects after ingestion of methyl parathion when compared with 15 controls (Czeizel 1994). A study that involved combined inhalation and dermal exposure of workers to methyl parathion showed no increase in chromosomal aberrations in their

lymphocytes (De Cassia Stocco et al. 1982). The results of available *in vivo* studies in animals (Degraeve et al. 1985; Grover and Malhi 1985; Huang 1973; Mathew et al. 1992; Tripathy et al. 1987; Waters et al. 1982) and the results of *in vitro* studies (Chen et al. 1981; Dean 1972; Degraeve et al. 1985; Gomez-Arroyo et al. 1987; Griffin and Hill 1978; Huang 1973; Kumar et al. 1993; Mohn 1973; Rashid and Mumma 1984; Shigaeva and Savitskaya 1981; Sobti et al. 1982; Waters et al. 1982) are equivocal.

Since *in vivo* tests in exposed human populations would involve concomitant exposure to other toxicants, it would be difficult to assess the genotoxic potential of methyl parathion alone. Therefore, additional well-designed *in vitro* studies using human cell lines are needed to determine the effects of methyl parathion on various genotoxic parameters (e.g., sister chromatid exchange, chromosomal aberrations, unscheduled DNA synthesis).

Reproductive Toxicity. No information is available in humans to indicate that methyl parathion affects reproductive function. No information is available on the reproductive effects in animals of inhaled or dermally administered methyl parathion. The limited available data indicate that methyl parathion is not toxic to male germ cells of mice following oral exposure (Degraeve et al. 1985; Waters et al. 1982), except possibly at very high doses (Mathew et al. 1992; Pagulayan et al. 1994). Also, negative data exist for histopathological effects on the reproductive system of dogs following ingestion of methyl parathion in the diet (Suba 1981). Additional studies in animals are needed to fully assess the reproductive toxicity of methyl parathion.

EPA (1988a) has discussed the results of two reproductive studies in rats. Results of these studies have not been presented in peer-reviewed scientific journals and are not available to the public. If these data become available, they will provide valuable information on the reproductive hazards of methyl parathion.

Developmental Toxicity. No information is available in humans to indicate that methyl parathion affects development. Rapid (within 30 minutes to 1 hour) placental transfer of methyl parathion has been demonstrated in rats following oral (Ackermann and Engst 1970) and dermal (Abu-Qare et al. 2000) administration to the dams. Oral studies in rats indicate that methyl parathion can induce subtle behavioral alterations in offspring at doses that do not induce clinical signs of maternal toxicity and can reduce acetylcholinesterase activity in maternal and fetal brain (Crowder et al. 1980; Gupta et al. 1985). Oral administration of methyl parathion to rat dams only during gestation or gestation and lactation did not affect electrocorticograms and evoked potentials in their offspring at 12 weeks of age, but similar

administration to the dams followed by direct administration to the offspring from weaning through 12 weeks of age did affect these end points in a dose-related manner (Desi et al. 1998). Although these studies indicate that methyl parathion may be a developmental neurotoxicant, all three studies have limitations of experimental design or reporting. No NOAEL was identified for the neurobehavioral effects and the dosing regimens were inadequate to demonstrate a dose response. The reporting of experimental design and results lacked detail in the electrophysiological study. A well-designed developmental neurotoxicity study is needed to confirm and extend these observations, and to define the dose-response and critical periods for neurotoxicity. There is some evidence of neurotoxicity in adult humans and animals from inhalation and dermal toxicity. If methyl parathion is confirmed as a developmental neurotoxicant by the oral route, it would likely be a developmental neurotoxicant by these routes as well. Further testing would be needed to confirm this.

Immunotoxicity. Only a single case report of skin allergy to methyl parathion has been reported in humans (Lisi et al. 1987). No studies are available in humans exposed to methyl parathion via the inhalation or oral route. Based on limited animal studies, immunotoxicity may be a sensitive end point of methyl parathion-induced toxicity (Shtenberg and Dzhunusova 1968; Street and Sharma 1975). Thus, humans may be at risk for adverse immunological effects following exposure to methyl parathion. The limited information available on the effects of combined exposure to methyl parathion suggest the its toxicity is not route-dependent. Therefore, there is no reason to suspect that the immunotoxic effects observed following oral exposure of animals are route-specific.

Some animal studies indicate that dietary exposure to methyl parathion causes decreased humoral and cellular responses (Shtenberg and Dzhunusova 1968; Street and Sharma 1975). A more recent, well-designed animal study that included a battery of immuno/lymphoreticular end points showed few effects at the nonneurotoxic doses tested (Crittenden et al. 1998). No adequate studies are available in humans to assess the immunotoxic potential of methyl parathion. Therefore, studies measuring specific immunologic parameters in occupationally exposed populations are needed to provide useful information. Further studies are also needed to investigate the mechanism for methyl parathion-induced immunotoxicity since this information would help to identify special populations at risk for such effects.

Neurotoxicity. Information in both humans and animals indicates that the nervous system is the major target of methyl parathion-induced toxicity following acute exposure by any route (Daly 1989; Dean et al. 1984; EPA 1978e; Fazekas 1971; Gupta et al. 1985; Nemec et al. 1968; Roberts et al. 1988; Suba 1984; Yamamoto et al. 1982; Youssef et al. 1987). The most prominent signs of acute exposure to methyl

parathion in humans via the oral and concomitant inhalation and dermal exposure routes are lethargy, nausea, vomiting, increased respiratory secretion, muscle fasciculations, and miosis (Dean et al. 1984). In rodents, oral exposure to methyl parathion causes convulsions, ataxia, abnormal gait, tremors, and behavioral impairment in offspring (EPA 1978e; Gupta et al. 1985; Miyamoto et al. 1963b; Suba 1984). Since the information available on the neurotoxic effects of methyl parathion indicates that the chemical behaves similarly across routes of exposure (Dean et al. 1984; EPA 1978e; Skinner and Kilgore 1982a, 1982b), it is unlikely that the neurotoxic effects observed following oral exposure are route-specific.

Neuropsychiatric disturbances have been seen in humans who had long-term exposure to high levels of organophosphates (Gershon and Shaw 1961); one case was associated with methyl parathion (Dille and Smith 1964). Moreover, the injection of methyl parathion into animals resulted in changes in brain components, such as increases in lipid content of the brain (Hasan and Khan 1985). Reliable information is lacking in humans on potential neurological effects of long-term, low-level exposure to methyl parathion as well as on potential long-term effects of acute high exposure to methyl parathion. This information can only be obtained from evaluation of cohorts exposed exclusively to methyl parathion, but data from subjects exposed to more than one organophosphate would still be helpful.

Epidemiological and Human Dosimetry Studies. The vast majority of reviewed literature concerning the health effects of methyl parathion in humans described case reports of occupational exposure or accidental or intentional ingestion of methyl parathion (Dean et al. 1984; Fazekas 1971; Fazekas and Rengei 1964; Rider et al. 1969; Rodnitzky et al. 1978). No epidemiological studies are available. The information on human exposure is limited because of the possible concurrent exposure to other chemicals, and the duration and the level of exposure to methyl parathion cannot be quantified from the information presented in these reports. Differences in formulation can also be a confounding factor. The most likely identifiable subpopulations exposed to methyl parathion are pesticide applicators, farm workers, individuals involved in the production of methyl parathion, or individuals exposed in recently and illegally sprayed homes or offices. Well-designed epidemiological studies of these exposed workers are needed. Specific assessments of cancer risks and examination of the effects of methyl parathion on the nervous, hematological, and immune systems would be important since these appear to be the major end points of toxicity in experimental animals. If methyl parathion causes adverse effects in any of these target organs or systems, then these human end points can be used to monitor methyl parathion exposure in individuals living near hazardous waste sites or in recently and illegally sprayed homes or offices.

Biomarkers of Exposure and Effect.

Exposure. Data are available on biomarkers of exposure of methyl parathion in humans and experimental animals. The data on the persistence of methyl parathion and its metabolites indicate that they are not reliable indicators for assessing long-term, low-level exposure (Abu-Qare et al. 2000; Dean et al. 1984; EPA 1978e; Fazekas 1971; Morgan et al. 1977; Ware et al. 1975) largely because methyl parathion is extensively metabolized and the metabolites are rapidly eliminated. Short-term (<1 day) biomarkers are total urinary 4-nitrophenol and alkyl phosphates (Morgan et al. 1977); these biomarkers are nonspecific. Blood methyl parathion is also a short-term biomarker (Abu-Qare et al. 2000; Ware et al. 1975) and is specific. Additional studies of the general population correlating methyl parathion metabolite levels with health status as well as with dietary habits would provide useful information for risk characterization and risk assessment.

Effect. There are no biomarkers of effects specific for methyl parathion. As an organophosphate pesticide, methyl parathion, in sufficient amounts, produces typical signs and symptoms of cholinergic stimulation. Plasma and RBC cholinesterase activities are widely used as biomarkers of exposure and effect for organophosphates, but alone, their levels do not predict whether adverse health effects will occur except in cases of significant inhibition. Data are available on cholinesterase levels in humans and animals following exposure to methyl parathion (Midtling et al. 1985; NIOSH 1976; Tafuri and Roberts 1987). Because baseline data for plasma and erythrocyte cholinesterase are not usually available for nonoccupationally exposed individuals, additional studies of normal values by age and sex are needed for assessing potential adverse effects. As mentioned under biomarkers of exposure, additional studies of the general population correlating methyl parathion metabolite levels with health status and dietary habits would be useful.

Absorption, Distribution, Metabolism, and Excretion. Evidence of absorption comes from the occurrence of toxic effects following exposure to methyl parathion by all three routes (Fazekas 1971; Miyamoto et al. 1963b; Nemec et al. 1968; Skinner and Kilgore 1982b). These data indicate that the compound is absorbed by both humans and animals. No information is available to assess the relative rates and extent of absorption following inhalation and dermal exposure in humans or inhalation in animals. A dermal study in rats indicates that methyl parathion is rapidly absorbed through the skin (Abu-Qare et al. 2000). Additional data further indicate that methyl parathion is absorbed extensively and rapidly in humans and animals via oral and dermal routes of exposure (Braeckman et al. 1983; Hollingworth et al. 1967; Ware et al. 1973). However, additional toxicokinetic studies are needed to elucidate or further examine the efficiency and kinetics of absorption by all three exposure routes.

Limited information from case reports is available regarding the distribution of methyl parathion in humans following dermal exposure with possible concomitant inhalation exposure (Ware et al. 1973, 1974, 1975). Following accidental oral or inhalation exposure to methyl parathion, clinical signs and symptoms or histopathological findings indicated that the compound was distributed to various tissues (Dean et al. 1984; Fazekas 1971; Fazekas and Rengei 1964). Although no quantitative information is available on the rate and extent of methyl parathion distribution in animals, the qualitative information for oral exposure does provide evidence as to the most likely target organs following both short- and long-term exposure (Galal et al. 1975; Gupta et al. 1985; Miyamoto et al. 1963b; Shtenberg and Dzhunusova 1968; Sonnenschein et al. 1989a, 1989b; Street and Sharma 1975; Williams et al. 1959). Only limited data exist for the distribution of methyl parathion in humans following dermal exposure. Information regarding distribution in animals following dermal exposure is available, but quantitative data may have been compromised since some degree of oral exposure may have also occurred (Abu-Qare et al. 2000). Therefore, additional data in animal studies are needed to determine the distribution and half-life in various tissues following inhalation, oral, dermal, and intravenous exposure.

The available information in humans regarding the metabolism of methyl parathion is limited to *in vitro* studies (Hollingworth et al. 1973). However, the *in vitro* (Benke and Murphy 1975; Benke et al. 1974; Hollingworth et al. 1973; Nakatsugawa et al. 1968; Neal and DuBois 1965) metabolic pathway of this chemical has been characterized in animals.

No studies were located regarding excretion of methyl parathion in humans following inhalation exposure. The limited information available from human case studies indicates that the chemical's metabolites are rapidly excreted primarily in the urine in humans following oral (Morgan et al. 1977) or dermal (Ware et al. 1974, 1975) exposure and in animals following oral (Hollingworth et al. 1973) or dermal (Abu-Qare et al. 2000) exposure.

Practically all toxicokinetic properties reported are based on the results from acute exposure studies. Generally, no information was available regarding intermediate or chronic exposure to methyl parathion. Because methyl parathion is an enzyme inhibitor, the kinetics of metabolism during chronic exposure could differ from those seen during acute exposure. Similarly, excretion kinetics may differ with time. Thus, additional studies on the distribution, metabolism, and excretion of methyl parathion and its toxic metabolite, methyl paraoxon, during intermediate and chronic exposure are needed to assess the potential for toxicity following longer-duration exposures.

Comparative Toxicokinetics. The data available on the toxicity of methyl parathion in humans are from acute exposure where neurotoxicity is the end point of concern (Dean et al. 1984; Fazekas 1971). This effect is also seen in animals after acute exposure (EPA 1978e; Miyamoto et al. 1963b; Yamamoto et al. 1982; Youssef et al. 1987). In addition, hepatic and gastrointestinal effects have also been observed in humans (Fazekas 1971; Fazekas and Rengei 1964) and animals (NCI 1979; Sonnenschein 1989a, 1989b). It is unclear whether these effects are primary or secondary. No toxicokinetic studies have been performed in humans, and information on the rate and extent of absorption, distribution, half-life in various animal tissues, and excretion is primarily limited to a single dermal study in a single animal species (Abu-Qare et al. 2000). Additional studies on the comparative toxicokinetics of both methyl parathion and methyl paraoxon by various routes of exposure are needed to resolve uncertainty associated in assessing the health risks.

Methods of Reducing Toxic Effects. There is good information on the procedures used to limit absorption and to interfere with the mechanism of action of methyl parathion after acute exposures (Aaron and Howland 1998; Bronstein and Currance 1988; EPA 1989b; Proctor et al. 1988; Stutz and Janusz 1988). However, no information is available on dealing with long-term, low-level exposures. This may be due, in part, to the limited information on toxic effects associated with such exposures. If additional information becomes available indicating adverse health effects of long-term exposures, then studies examining methods for mitigating the effects of such exposures would become a data need.

Children's Susceptibility. Present information indicates a potential for age-related differences in susceptibility to methyl parathion. However, data are limited in both human and animal studies. In future incidents involving methyl parathion poisoning of both children and adults, better estimates should be made on exposure levels, exposure routes, and urinary metabolite levels relative to the observed symptoms of toxicity. Additional animal studies are needed to further investigate the effects of methyl parathion on developing nervous systems. Other studies could compare neurological effects in immature animals of various ages with those seen in adults, particularly via the oral or inhalation exposure routes. Specific data needs relating to both pre- and postnatal exposures and development are discussed above under Developmental Toxicity. Furthermore, metabolic pathways and enzymatic activity for methyl parathion should be more clearly elucidated since potential age-related differences in the ability to metabolize methyl parathion could result in age-related differences in toxicity; suggestive evidence of age-related differences in metabolism was reported in rats (Benke and Murphy 1975). 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 methyl parathion. No information was located regarding pediatric-specific

methods for reducing peak absorption following exposure to methyl parathion or reducing body burden. The information available indicates that methods to reduce peak absorption of methyl parathion and to interfere with the mechanism of action used for intoxication in adults are applicable to children. Developmental studies in animals are needed to quantitatively measure placental transfer of methyl parathion, to determine whether methyl parathion can be metabolized by placental tissue, and to further evaluate the transfer of methyl parathion and its metabolites to breast milk.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

A study of the dermal toxicokinetics of methyl parathion in female rats, sponsored by ATSDR, is being conducted at the University of Mississippi Medical Center. The principal investigator is Dr. Ing K. Ho, Department of Pharmacology and Toxicology, 500 North State Street, Jackson, Mississippi 39216-4505.

ATSDR is conducting a health study to investigate the lasting health effects of methyl parathion exposure on children. In this study, ATSDR will be testing children in two states, Ohio and Mississippi. The principal Investigator is Dr. Rubina Imtiaz, ATSDR Division of Health Studies, 1600 Clifton Road, Atlanta, Georgia 30333.