2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of diethyl phthalate and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and describes levels of significant exposure for diethyl phthalate based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals 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 a figure. The points in the figure 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. These distinctions are intended to help-users of the documents identify levels of exposure at which adverse health effects start to appear. They should also help to determine 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 tables and figures may differ depending on the user’s perspective. For example, physicians concerned with the interpretation of clinical findings in

exposed persons may be interested in levels of exposure associated with “serious” effect. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability and extrapolation of data from laboratory animals and humans.

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

2.2.1 Inhalation Exposure

No studies were located regarding the following health effects in humans or animals following inhalation exposure to diethyl phthalate.

2.2.1.1 Death

2.2.1.2 Systemic Effects

2.2.1.3 Immunological and Lymphoreticular Effects

2.2.1.4 Neurological Effects

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals following inhalation exposure to diethyl phthalate.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans following oral exposure to diethyl phthalate.

The lowest lethal doses of diethyl phthalate in rabbits and guinea pigs administered the compound by gavage were determined to be 4,000 and 5,000 mg/kg, respectively (Smyth and Smyth 1931). However, this study is limited in that only two to six animals were tested at each dose level and no control data were presented. Furthermore, neither the clinical signs exhibited by the animals nor the cause(s) of death were stated. No deaths were observed when diethyl phthalate was incorporated into the diet of mice for 2 weeks at doses of up to 6,500 mg/kg/day. Thus, based on this information, it would appear that diethyl phthalate is relatively nonlethal to orally exposed experimental animals.

2.2.2.2 Systemic Effects

No studies were located regarding dermal effects in humans or animals following oral exposure to diethyl phthalate.

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

Respiratory Effects. No studies were located regarding respiratory effects in humans following oral exposure to diethyl phthalate. Two-to-16-week dietary administration of diethyl phthalate, at concentrations up to 3,710 mg/kg/day, had no effect on the gross or microscopic pathology of the lungs or trachea in rats (Brown et al. 1978).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following oral exposure to diethyl phthalate. Two-to-16-week dietary administration of diethyl phthalate, at concentrations up to 3,710 mg/kg/day, had no effect on the gross or microscopic pathology of the hearts or aorta in rats. Administration of 3,160 mg/kg/day to male rats resulted in a statistically significant ($p<0.01$) increase in heart weight (Brown et al. 1978).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following oral exposure to diethyl phthalate. Two-to-16-week dietary administration of high concentrations of diethyl phthalate resulted in enlarged stomachs, small intestines, and/or caecums. No evidence of histological damage was found in any gastrointestinal tissue. The investigators did not consider the effects treatment-related (Brown et al. 1978).

Hematological Effects. No studies were located regarding hematological effects in humans following oral exposure to diethyl phthalate. A statistically significant increase in erythrocyte counts was reported in male rats receiving 3,160 mg/kg/day (5% in diet) diethyl phthalate in the diet for 6 weeks. However, this change was no longer apparent after 16 weeks of dietary administration. In addition, no treatment-related effects were noted in packed cell volume, reticulocyte counts, or leukocyte counts in male or female rats in this study (Brown et al. 1978).

TABLE 2-1. Levels of Significant Exposure to Diethyl Phthalate - Oral

Key[a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)		LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Systemic								
1	Rat CD	2 wk ad lib (F)	Resp	3160 3710	M F			Brown et al. 1978
			Cardio	3160 3710	M F			
			Gastro	3160 3710	M F			
			Hemato	3160 3710	M F			
			Musc/skel	3160 3710	M F			
			Hepatic	3160 3710	M F			
			Renal	3160 3710	M F			
			Endocr	3160 3710	M F			
			Ocular	3160 3710	M F			
			Bd Wt	3160 3710	M F			
2	Rat Sprague-Dawley	4 d 1x/d (GO)	Bd Wt	1600	M			Foster et al. 1980
3	Mouse Cd-1	14 d ad lib (F)	Bd Wt	3250		6500	(> 10% decrease in body weight)	NTP 1984

TABLE 2-1. Levels of Significant Exposure to Diethyl Phthalate - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
Immuno/Lymphoret							
4	Rat CD	2 wk ad lib (F)		3160 M 3710 F			Brown et al. 1978
Neurological							
5	Rat CD	2 wk ad lib (F)		3160 M 3710 F			Brown et al. 1978
Reproductive							
6	Rat CD	2 wk ad lib (F)		3160 M 3710 F			Brown et al. 1978
7	Rat Sprague-Dawley	1-4 d 1x/d (GO)		1600 M			Foster et al. 1983
8	Rat Wistar	10 d 1x/d (GO)		1600 M			Gray and Butterworth 1980
9	Rat Wistar	1 x/d 2d (F)			2000 [b] M (mitochondrial swelling with focal dilation; Leydig cell SER vesiculation)		Jones et al. 1993
10	Rat Wistar	1 wk ad lib (F)		1000 M			Oishi and Hiraga 1980

TABLE 2-1. Levels of Significant Exposure to Diethyl Phthalate - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)		LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)	Reference
Developmental									
11	Rat Sprague-Dawley	10 d Gd 6-15 ad lib (F)		1910	F	3210	F (increased incidence of supernumerary ribs)		Field et al. 1993
12	Mouse CD-1	6 d Gd 6-13 1x/d (GO)		4500	F				Hardin et al. 1987
INTERMEDIATE EXPOSURE									
Systemic									
13	Rat CD	16 wk ad lib (F)	Resp	3160	M				Brown et al. 1978
				3710	F				
			Cardio	3160	M				
				3710	F				
			Gastro	3160	M				
				3710	F				
			Hemato	3160	M				
				3710	F				
			Musc/skel	3160	M				
				3710	F				
			Hepatic	3160	M				
				3710	F				
			Renal	3160	M				
				3710	F				
			Endocr	3160	M				
				3710	F				
			Ocular	3160	M				
				3710	F				
			Bd Wt	3160	M				
				3710	F				

TABLE 2-1. Levels of Significant Exposure to Diethyl Phthalate - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
14	Rat F-344	3 wk (F)	Hepatic		1753 [c] M (slight increase in liver weights and activity of peroxisomal enzymes; mild peroxisomal proliferation)		Moody and Reddy 1978
15	Mouse CD-1	NS ad lib (F)	Bd Wt	1625 M 3250 F	3250 M (body weight gain inhibition of > 10%)		Lamb et al. 1987
Immuno/Lymphoret							
16	Rat CD	16 wk ad lib (F)		3160 M 3710 F			Brown et al. 1978
Neurological							
17	Rat CD	16 wk ad lib (F)		3160 M 3710 F			Brown et al. 1978
Reproductive							
18	Rat CD	16 wk ad lib (F)		3160 M 3710 F			Brown et al. 1978
19	Mouse CD-1	NS ad lib (F)				3250 (< number of pups)	Lamb et al. 1987

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

[b]Used to derive an acute oral Minimal Risk Level (MRL) of 7 mg/kg/day; dose was divided by an uncertainty factor of 300 (3 for the conversion of a minimal LOAEL to a NOAEL, 10 for interspecies extrapolation, and 10 for human variability).

[c]Used to derive an intermediate oral MRL of 6 mg/kg/day; dose was divided by an uncertainty factor of 300 (3 for the conversion of a minimal LOAEL to a NOAEL, 10 for interspecies extrapolation, and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = female(s); Gastro = gastrointestinal; (GO) = gavage in oil; Gd = gestation day; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed- adverse-effect level; M = male(s); Musc/skel = musculoskeletal; NOAEL = no-observed- adverse-effect level; NS = not specified; Resp = respiratory; SER = smooth endoplasmic reticulum; wk = week(s); x = time(s)

Figure 2-1. Levels of Significant Exposure to Diethyl Phthalate – Oral (continued)

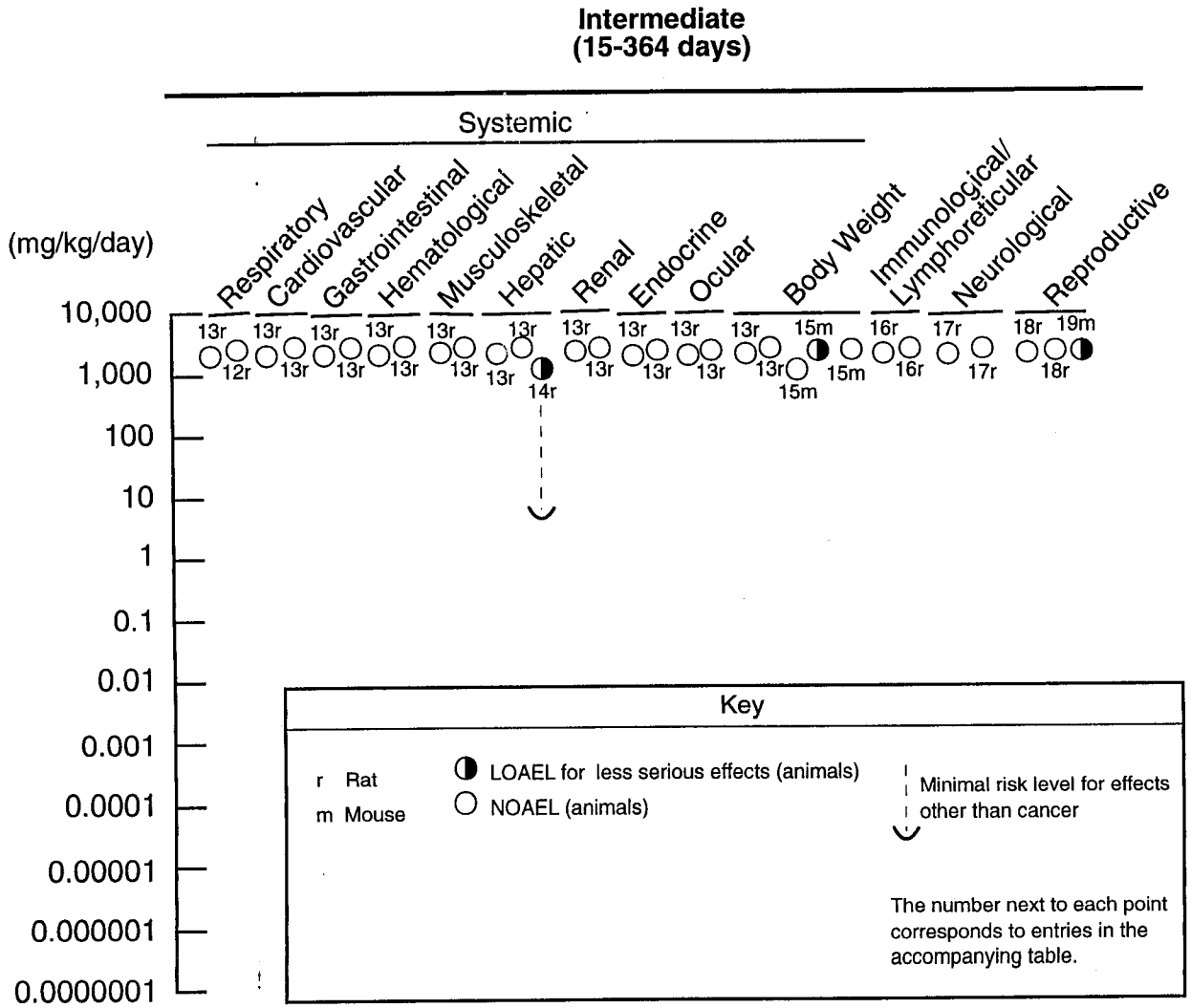
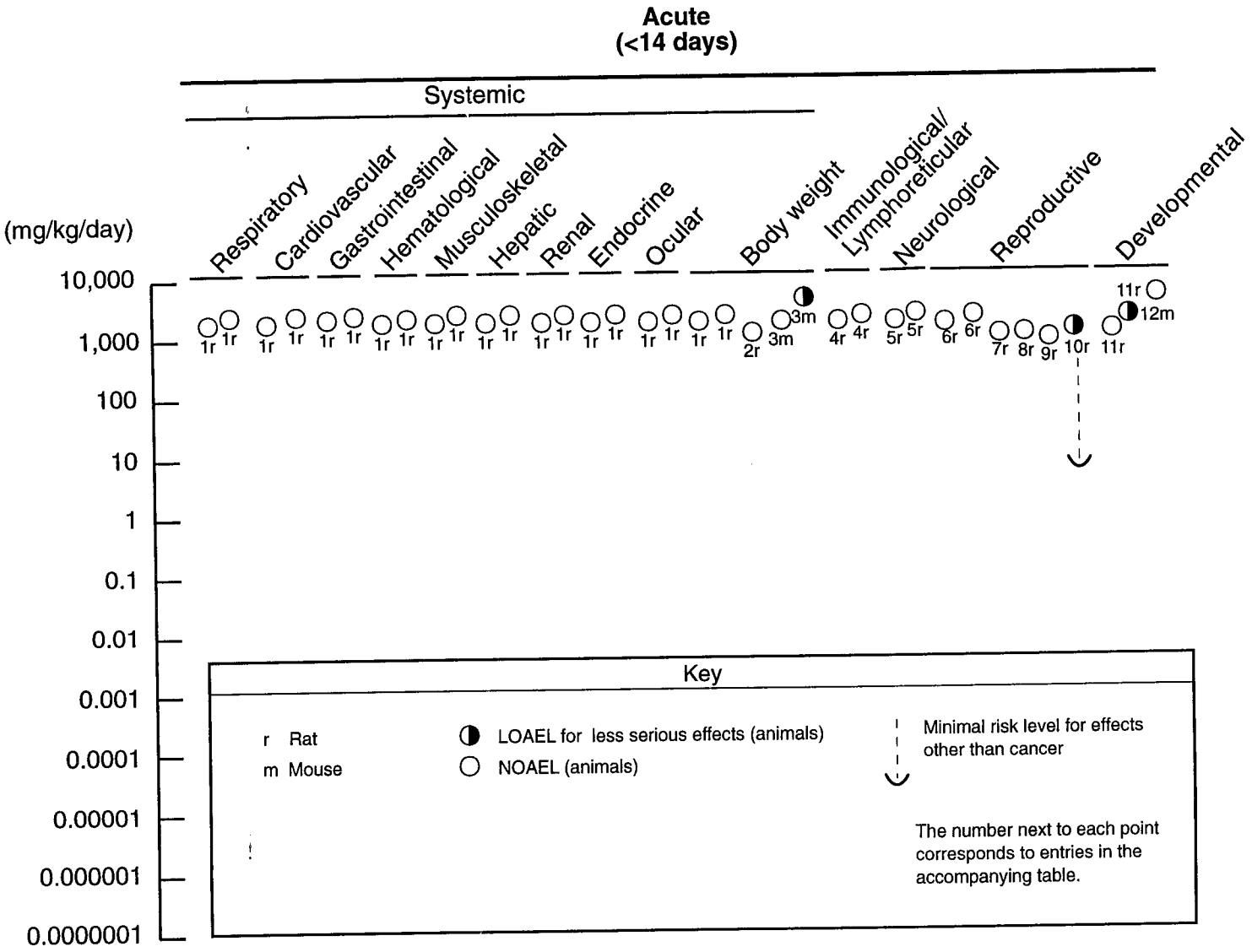


Figure 2-1. Levels of Significant Exposure to Diethyl Phthalate – Oral



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Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following oral exposure to diethyl phthalate. Two-to-l6-week dietary administration of diethyl phthalate, at concentrations up to 3,710 mg/kg/day, had no effect on the gross or microscopic pathology of skeletal muscle in rats (Brown et al. 1978).

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to diethyl phthalate. A number of studies have reported increases in absolute and relative liver weights in animals administered up to 3,710 mg/kg/day diethyl phthalate in the diet for an acute exposure duration (Brown et al. 1978; Oishi and Hiraga 1980). However, in the absence of biochemical, functional, or histopathological evidence of liver damage, the toxicological significance of these changes in liver weight is not known. Only slight, but statistically significant, increases in liver weight, hepatic peroxisome, and hepatic catalase and camitine acetyltransferase activities occurred in rats administered 1,753 mg/kg/day diethyl phthalate in the diet for 3 weeks (Moody and Reddy 1978). These changes were minor compared to changes observed after dietary administration of di-(2-ethylhexyl)phthalate, di-(2-ethylhexyl)adipate, or di-(2-ethylhexyl)sebacate. Nevertheless, the observed changes are considered a less serious LOAEL and were used to derive an intermediate-duration MRL of 6 mg/kg/day, as described in Section 2.4.

Fatty degeneration and slight vacuolation were noted in the liver of some animals fed diethyl phthalate for up to 16 weeks (Brown et al. 1978). However, although no incidence data were provided, the investigators stated that these changes were not dose related. A dose-related increase in the incidence of congestion, cloudy swelling, and scant, moderate, or abundant glycogen was noted in guinea pigs administered 250-1,000 mg/kg/day diethyl phthalate in the feed for l-3 months (Smyth and Smyth 1932). This study is limited, however, in that only two to four animals were tested at each dose.

Based on the available information, it appears that while diethyl phthalate can induce an increase in relative liver weight in experimental animals, the absence of any treatment-related biochemical, functional, or histopathological changes in the liver suggests that the increase in liver weight may be due to exposure to high oral concentrations rather than to a direct toxic effect of diethyl phthalate.

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Renal Effects. No studies were located regarding renal effects in humans after oral exposure to diethyl phthalate.

An increase in relative kidney weight was observed in male rats administered 5% diethyl phthalate in the diet for 2 weeks, and in male and female rats administered 5% diethyl phthalate in the diet for 16 weeks (Brown et al. 1978). The approximate daily intakes (listed by the authors) were 3,160 mg/kg/day for male rats and 3,710 mg/kg/day for female rats. There was no evidence that these organ weight changes were accompanied by any biochemical, functional, or histopathological renal damage. Therefore, the toxicological significance of this change in kidney weight is not known.

Congestion, cloudy swelling of the tubules, and desquamation were noted in guinea pigs administered 250-1,000 mg/kg/day diethyl phthalate in the feed for l-3 months (Smyth and Smyth 1932). This study is limited, because only three or four animals were tested at each dose.

Based on the available information, it appears that while diethyl phthalate can induce an increase in relative kidney weight in experimental animals, the absence of any reliable treatment-related biochemical, functional, or histopathological changes in the kidney suggests that the increase in kidney weight was probably not due to a direct toxic effect of diethyl phthalate.

Endocrine Effects. No studies were located regarding endocrine effects in humans following oral exposure to diethyl phthalate. Two-to-16-week dietary administration of diethyl phthalate, at concentrations up to 3,710 mg/kg/day, had no effect on the gross or microscopic pathology of the pituitary, adrenals, thyroid, or pancreas in rats. Relative organ weights of the adrenals, pituitary, and thyroid were slightly to moderately elevated at 3,160 mg/kg/day in males (Brown et al. 1978).

Ocular Effects. No studies were located regarding ocular effects in humans following oral exposure to diethyl phthalate. Two-to-16-week dietary administration of diethyl phthalate, at concentrations up to 3,710 mg/kg/day, had no effect on the gross or microscopic pathology of the eye (Brown et al. 1978).

Body Weight. No studies were located regarding body weight changes in humans following oral exposure to diethyl phthalate.

A number of studies have reported significant (>l0%) decreases in body weight gain in experimental animals after acute- and intermediate-duration dietary exposure (Brown et al. 1978; Lamb et al. 1987; NTP 1984). In at least one study, the results of a concurrent paired-feeding experiment indicated that the inhibition was primarily attributable to lower food consumption and/or poorer food utilization, rather than to a direct toxic action of diethyl phthalate (Brown et al. 1978). In a continuous breeding study with mice, dietary administration of the equivalent of 3,250 mg/kg/day was associated with a 47% weight gain inhibition (Lamb et al. 1987).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans following oral exposure to diethyl phthalate. Two-to-16-week dietary administration of diethyl phthalate, at concentrations up to 3,710 mg/kg/day, had no effect on the gross or microscopic pathology of (unspecified) lymph nodes or the thymus (Brown et al. 1978).

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following oral exposure to diethyl phthalate. Two-to-16-week dietary administration of diethyl phthalate, at concentrations up to 3,710 mg/kg/day, had no effect on the gross or microscopic pathology of the brain or the sciatic nerve (Brown et al. 1978). Exposure to 3,160 mg/kg/day (males) or 3,710 mg/kg/day (females) resulted in increased relative brain weights (Brown et al. 1978).

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to diethyl phthalate.

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Several investigators have studied the effects of diethyl phthalate on male reproductive function in rats since other phthalic acid esters have been shown to be toxic to the male reproductive system (ATSDR 1989; Foster et al. 1980, 1983; Gray and Butterworth 1980; Oishi and Hiraga 1980). Testicular and accessory gland weight and histopathology were unaffected by treatment of male rats with diethyl phthalate at doses up to 1,600 mg/kg/day (Foster et al. 1980; Gray and Butterworth 1980; Oishi and Hiraga 1980). In addition, diethyl phthalate had no effect on progesterone binding to testes microsomes, testicular cytochrome P-450 content, or testicular steroidogenic enzyme activity, whereas other phthalates known to cause testicular toxicity have induced changes in these parameters (Foster et al. 1983). The authors concluded that the lack of effect on these parameters is consistent with the lack of morphological effects on the testes reported in other studies.

Acute administration of 2,000 mg/kg/day diethyl phthalate produced ultrastructural evidence of Leydig cell mitochondrial swelling, and both focal dilatation and vesiculation of the smooth endoplasmic reticulum (Jones et al. 1993). These findings are considered a less serious LOAEL and were used to derive an acute oral MRL of 7 mg/kg/day (see Section 2.4).

In a continuous breeding study in CD-l mice, dietary administration of 2.5% diethyl phthalate (>99% pure) (3,250 mg/kg/day) produced physiological effects in F_1 parental animals and significantly decreased the number of live pups per litter (Lamb et al. 1987). No adverse effects on the physiology, fertility, or reproductive performance of the F_0 generation animals were observed. The F_0 mice were fed diets containing the test compound at concentrations of 0, 325, 1,625, or 3,250 mg/kg daily during premating, mating, gestation, and lactation; the F_1 generation animals received 0 or 3,250 mg/kg/day on the same regimen.

The parental toxicity in the F_1 generation was evidenced by a significant decrease in body weight, increased prostate weight in males, and increased liver and pituitary weights in females. However, histological findings in the liver and pituitary were not reported, rendering the toxicological significance of a change in these organ weights uncertain. Although a significant decrease in sperm concentration occurred in the males, no adverse effect on the fertility was observed. The total number of live pups per litter in the F_1 generation was significantly lower by 14% in the test group compared to the controls. The study limitations include a lack of data on the histopathological findings of the

tissues and failure to assess the effects of the test compound on the F_1 generation at the two lower doses. Data on the F, generation showed an increase in the number of live pups per litter at the low doses. As a result, no NOAEL was established.

Administration of up to a dose equivalent of 3,710 mg/kg/day diethyl phthalate was associated with no gross or microscopic evidence of histopathological damage to the gonads, uterus, or the prostate and seminal vesicles of rats. Relative testes weights were significantly elevated at a dose equivalent of 3,160 mg/kg/day (Brown et al. 1978).

The highest NOAEL value and the LOAEL value for reproductive effects for each species and duration category are recorded in Table 2-l and plotted in Figure 2-1.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to diethyl phthalate.

A study in mice reported no significant evidence of maternal toxicity or neonatal developmental effects due to oral administration of 4,500 mg/kg/day on gestation days 6-13 (Hardin et al. 1987). Newborn mice were evaluated for survival, birth weight, and weight gain. A limitation of this study was that these results were determined by use of a proposed short-term in *vivo* developmental toxicity assay, and no comparison of this method to conventional assays was available. In rats, dietary administration of up to 2.5% diethyl phthalate (1,910 mg/kg/day) produced no embryonic or fetotoxic effects. At a dietary level of 5% (3,210 mg/kg/day), treated embryos had an increased number of skeletal variations, particularly rudimentary (supernumerary) ribs (Field et al. 1993). However, the significance of this finding is obscured by the high incidence of skeletal variations in the controls and the reduced food and water consumption of the high-dose dams early in gestation.

The NOAEL value and LOAEL value for developmental effects after acute exposure to diethyl phthalate are recorded in Table 2-1 and plotted in Figure 2-l.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to diethyl phthalate.

Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals following oral exposure to diethyl phthalate.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans following dermal exposure to diethyl phthalate. At daily application doses of up to 100 μL (mice) or 300 μL (rats), equivalent to 772 mg/kg/day (mice) and 855 mg/kg/day (rats), diethyl phthalate did not produce an increased mortality incidence when administered 5 days per week for 2 years (NTP 1993 [board draft]).

2.2.3.2 Systemic Effects

No studies were located regarding musculoskeletal effects in humans or animals following dermal exposure to diethyl phthalate.

The highest NOAEL values and all reliable LOAEL values for systemic effects for each species and duration category are recorded in Table 2-2.

TABLE 2-2. Levels of Significant Exposure to Diethyl Phthalate - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
ACUTE EXPOSURE						
Systemic						
Rabbit New Zealand	once	Ocular	0.1m washed			Dear and Jassup 1978
Rabbit New Zealand	once	Ocular		0.1mL not washed	(minimally irrating)	Dear and Jassup 1978
Immuno/Lymphoret						
Human	5x		0.1 mL			Greif 1967
INTERMEDIATE EXPOSURE						
Systemic						
Rat F344	4 w 5d/w	Resp	1715			NTP 1993
		Cardio	1715			
		Gastro	1715			
		Hemato	1715			
		Hepatic	1715			
		Renal	1715			
		Endocr	1715			
		Derm	1715			
		Bd Wt	1715			
Mouse B6C3F1	4 w 5d/w	Resp	3740			NTP 1993
		Cardio	3740			
		Gastro	3740			
		Hepatic	3740			
		Renal	3740			
		Endocr	3740			
		Derm	3740			
		Bd Wt	3740			

TABLE 2-2. Levels of Significant Exposure to Diethyl Phthalate - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
Rat B6C3F1	103 w 5d/w	Resp	772			NTP 1993
		Cardio	772			
		Gastro	772			
		Hemato	772			
		Hepatic	772			
		Renal	772			
		Endocr	772			
		Derm	772			
		Bd Wt	772			
Immuno/Lymphoret						
Rat F344/N	103 w 5d/w		855			NTP 1993
Mouse B6C3F1	103 w 5d/w		772			NTP 1993
Neurological						
Rat F344/N	103 w 5d/w		855			NTP 1993
Mouse B6C3F1	103 w 5d/w		772			NTP 1993
Reproductive						
Rat F344/N	103 w 5d/w		855			NTP 1993
Mouse B6C3F1	103 w 5d/w		772			NTP 1993

TABLE 2-2. Levels of Significant Exposure to Diethyl Phthalate - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
Immuno/Lymphoret						
Rat F344	4 w 5d/w		1715			NTP 1993
Mouse B6C3F1	4 w 5d/w		3740			NTP 1993
Neurological						
Rat F344	4 w 5d/w		1715			NTP 1993
Mouse B6C3F1	4 w 5d/w		3740			NTP 1993
Reproductive						
Rat F344	4 w 5d/w		1715			NTP 1993
Mouse B6C3F1	4 w 5d/w		3740			NTP 1993
CHRONIC EXPOSURE						
Systemic						
Rat F344/N	103 w 5d/w	Resp	855			NTP 1993
		Cardio	855			
		Gastro	855			
		Hemato	855			
		Hepatic	855			
		Renal	855			
		Endocr	855			
		Derm	855			
		Bd Wt	855			

TABLE 2-2. Levels of Significant Exposure to Diethyl Phthalate - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
				Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Cancer						
Rat F344/N	103 w 5d/w					NTP 1993
Mouse B6C3F1	103 w 5d/w					NTP 1993

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Derm = dermal; Endocr = endocrine; Gastro = gastrointestinal; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse effect; NOAEL = no-observed- adverse-effect level; Resp = respiratory; wk = week(s); x = time(s)

Respiratory Effects. No studies were located regarding respiratory effects in humans following dermal exposure to diethyl phthalate.

Repeated dermal administration of diethyl phthalate had no adverse effects on lung histopathology in rats or mice exposed for 4 weeks or 2 years (NTR 1993 [board draft]).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following dermal exposure to diethyl phthalate.

Repeated dermal administration of diethyl phthalate had no adverse effects on heart histopathology in rats or mice exposed for 4 weeks or 2 years (NTP 1993 [board draft]).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following dermal exposure to diethyl phthalate.

Repeated dermal administration of diethyl phthalate had no adverse effects on the histopathology of the esophagus, gallbladder (mouse only), large intestine, small intestine, stomach, or bladder in rats or mice exposed for 4 weeks or 2 years (NTP 1993 [board draft]).

Hematological Effects. No studies were located regarding hematological effects in humans following dermal exposure to diethyl phthalate.

The results of studies in rats and mice indicated no adverse effects on standard hematological parameters after repeated dermal application of 100% diethyl phthalate (NTR 1993 [board draft]).

Hepatic Effects. No studies were located regarding hepatic effects in humans following dermal exposure to diethyl phthalate.

Repeated dermal administration of diethyl phthalate had no adverse effects on liver histopathology in rats or mice exposed for 4 weeks or 2 years (NTP 1993 [board draft]). In 4-week studies, administration of diethyl phthalate did result in increased relative liver weights in both sexes of rats and in female mice. However, no adverse effects on clinical indices of liver function were noted (NTP 1993 [board draft]).

Renal Effects. No studies were located regarding renal effects in humans following dermal exposure to diethyl phthalate.

Repeated dermal administration of diethyl phthalate had no adverse effects on kidney histopathology in rats or mice exposed for 4 weeks or 2 years (NTP 1993 [board draft]). In 4-week studies, administration of diethyl phthalate did result in increased relative kidney weights in both sexes of rats. However, no adverse effect on clinical indices of kidney function were noted (NTP 1993 [board draft]).

Dermal Effects. No studies were located regarding dermal effects in humans following dermal exposure to diethyl phthalate.

Diethyl phthalate was shown to be very slightly or slightly irritating when applied repeatedly to the intact or abraded skin, respectively, of an unidentified species (Dow Chemical 1952). However, the criteria to judge irritation were not specified in this study, and none of the protocol details were provided. Other data indicate that chronic dermal diethyl phthalate administration is associated with mild, nonadverse dermal acanthosis in rats (NTP 1993 [board draft]). One study reported that diethyl phthalate caused intradermal irritation evidenced by the presence of inflammation at the site of injection in the skin.of rabbits (Galley et al. 1966).

Ocular Effects. No studies were located regarding ocular effects in humans following dermal exposure to diethyl phthalate.

Ocular irritation tests conducted in rabbits indicate that diethyl phthalate is not a primary ocular irritant (Dear and Jassup 1978; Lawrence et al. 1975). The compound caused minimal irritation when applied to the eye without washing, and was practically non-irritating when the eye was washed after instillation (Dear and Jassup 1978).

Body Weight Effects. No studies were located regarding body weight effects in humans following dermal exposure to diethyl phthalate.

In 2-year rat dermal toxicity studies, diethyl phthalate produced slight body weight gain decrements in male and female rats. The equivalent doses administered were 285 and 855 mg/kg/day. Diethyl phthalate had no effect on body weight gain in 4-week rat and mouse studies or in 2-year mouse studies (NTP 1993 [board draft]).

2.2.3.3 Immunological and Lymphoreticular Effects

In a factory that produces shoes from polyvinyl chloride granulate (which contains a compound the authors called dioctyl phthalate, but which is probably di-[2-ethylhexyllphthalate), 30 workers with dermatitis and 30 workers without dermatitis were patch tested with diethyl phthalate and compared with 30 controls that had no known exposure to polyvinyl chloride or phthalates (Vidovic and Kansky 1985). One worker of the 30 with dermatitis and 1 of the 30 without dermatitis responded positively with an allergic contact response to diethyl phthalate. None of the controls had a positive response. The authors concluded that the results in the exposed worker populations indicate that the phthalates are sensitizers, and that the positive reaction to diethyl phthalate was most likely due to cross-sensitization with dioctyl phthalate since very little diethyl phthalate is present in polyvinyl chloride (Vidovic and Kansky 1985). In a skin patch test designed to maximize sensitization, none of 25 healthy adult volunteers showed a positive reaction to diethyl phthalate (Greif 1967).

The NOAEL and LOAEL values for immunological or lymphoreticular effects in humans following dermal exposure are recorded in Table 2-2.

Repeated dermal administration of diethyl phthalate had no adverse effects on the histopathology of the spleen, thymus, or lymph nodes or on thyroid weight in rats or mice exposure for 4 weeks or 2 years (NTP 1993 [board draft]).

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans following dermal exposure to diethyl phthalate. In 4-week and 2-year studies with rats and mice, diethyl phthalate had no adverse effect on the histopathology or weight of the brain (NTP 1993 [board draft]). These NOAEL values are recorded in Table 2-2.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following dermal exposure to diethyl phthalate.

In 4-week and 2-year studies with rats and mice, diethyl phthalate had no adverse effect on the histopathology of male or female reproductive organs (NTP 1993 [board draft]). These NOAEL values are recorded in Table 2-2.

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following dermal exposure to diethyl phthalate.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following dermal exposure to diethyl phthalate.

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans following dermal exposure to diethyl phthalate.

The results of a board draft study indicated that male and female rats receiving 100 or 300 µL diethyl phthalate (approximately 285 mg/kg/day or 855 mg/kg/day), applied to the intrascapular skin 5 days per week for 2 years, did not develop any evidence of carcinogenic activity. Equivocal evidence of carcinogenicity was found in both sexes of mice dermally exposed to up to 30 µL diethyl phthalate/day, 5 days per week for 2 years. The incidences of combined hepatocellular adenoma/carcinoma in the male mice dosed with 0, 7.5, 15, and 30 µL/day (corresponding to 0, 193, 386, and 772 mg/kg/day) were 9/50, 14/50, 14/50, and 18/50, respectively. The corresponding incidences in the female mice were 7/50, 16/51, 19/50, and 12/50, respectively (NTP 1993 [board draft]). Because of the absence of a dose-response relationship, these data are not adequate for the determination of a cancer effect level. Finally, diethyl phthalate had no tumor initiation or promoting capability in l-year mouse studies (NTP 1993 [board draft]).

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding absorption of diethyl phthalate in humans or animals following inhalation exposure.

2.3.1.2 Oral Exposure

No studies were located regarding the absorption of diethyl phthalate in humans or animals following oral exposure.

2.3.1.3 Dermal Exposure

No *in vivo* studies were located regarding the absorption of diethyl phthalate in humans following dermal exposure. The absorption of diethyl phthalate has been measured *in vitro* through human (from abdominal skin) and rat (from dorsal region) epidermal membranes set up in flow-through diffusion cells (Hotchkiss et al. 1992; Mint et al. 1992; Scott et al. 1987). The extent of percutaneous absorption 72 hours after application to intact, unoccluded human skin was 4.8% of the applied dose (Hotchkiss et al. 1992). Application of diethyl phthalate to the epidermal membranes for 8 hours resulted in a lag phase of absorption followed by a linear phase. Steady-state absorption rates determined for diethyl phthalate for human and rat epidermal membranes showed that diethyl phthalate was absorbed more slowly through human epidermal membranes than through rat epidermal membranes. For humans, the steady-state absorption rate for diethyl phthalate was 1.27 ± 0.11 μg/cm^2/hour. The steady-state absorption rate for rats was 41.37 ± 9.28 μg/cm^2/hour. The human lag time was 6 hours while the lag time for rats was 1 hour. Rat epidermal membrane was more permeable to diethyl phthalate than the human epidermal membrane. The permeability constant of diethyl phthalate for humans was 1.14×10^{-5} cm/hour and for rats it was 37×10^{-5} cm/hour. Dermal application of diethyl phthalate to the human epidermis produced no more skin damage than dermal application of water did. The authors reported that the differences in absorption between the human and rat membranes are to be expected because of the complex differences in the biochemical and structural composition of the two membranes (Scott et al. 1987). These results have been confirmed by additional *in vitro* studies that reported 72-hour absorptions of 36.9% and 5.6% of the applied doses in unoccluded rat and human skin preparations, respectively (Mint et al. 1992).

In rodents, diethyl phthalate is absorbed following dermal exposure. The extent of dermal absorption of diethyl phthalate -was studied using a single dermal application of radiolabeled (^{14}C) diethyl phthalate (5-8 mg/cm^2) to the clipped skin of male rats (Elsisi et al. 1989). The amount of ^{14}C radioactivity excreted was taken as an index of the percutaneous absorption. Twenty-four percent of the dose was excreted in the first 24 hours. The rate of excretion then decreased so that only 11% of the dose was excreted in the next 24 hours. A cumulative total of 50% of the dose was excreted by 7 days, with urinary excretion volumes exceeding fecal volumes (quantitative data not provided).

Seven days after exposure, 34% of the label was in the area of application and 4.8% was in the plastic cap used to protect the application site. Seven other phthalate esters were also tested in the study: dimethyl, dibutyl, dihexyl, di(2-ethylhexyl), diisodecyl, and benzyl butyl phthalates. The results indicated that the length of the side chain affected the dermal uptake of phthalate esters. Skin absorption was inversely proportional to the side chain length-the longer the chain (more than four carbons), the lesser the dermal uptake (Elsisi et al. 1989).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding the distribution of diethyl phthalate in humans or animals following inhalation exposure.

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of diethyl phthalate in humans or animals following oral exposure.

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of diethyl phthalate in humans following dermal exposure.

Results of an experiment in which rats were exposed dermally to a single application of ^{14}C-diethyl phthalate (5-8 mg/cm^2) showed that distribution of the radioactivity is wide but that diethyl phthalate and/or its metabolites are not likely to accumulate to any great extent in tissues (Elsisi et al. 1989). Very little of the ^{14}C radioactivity was found in the tissues 1 week after exposure to diethyl phthalate. The amounts of label found in the brain, lung, liver, spleen, small intestine, kidney, testis, spinal cord, and blood were each less than 0.5% of the administered dose. Adipose tissue, muscle, and skin accounted for 0.03%, 0.14%, and 0.06% of the administered ^{14}C radioactivity, respectively. Thirty-

four percent remained in the area of application, and 4.8% remained in the plastic cap used to protect the application site (Elsisi et al. 1989).

2.3.2.4 Other Routes of Exposure

No studies were located regarding the distribution of diethyl phthalate in humans following exposure by other routes.

^{14}C-diethyl phthalate was administered intraperitoneally (2,800 mg/kg) to pregnant rats on either day 5 or day 10 of gestation (Singh et al. 1975). Results showed that radioactivity from ^{14}C-diethyl phthalate is transmitted across the placenta from mother to fetus for at least 15 days postinjection. ^{14}C radioactivity was widely distributed and was detected (<l%) in maternal blood, placenta, amniotic fluid, and developing fetuses at all gestational stages investigated (Singh et al. 1975).

2.3.3 Metabolism

No *in vivo* studies were located regarding the metabolism of diethyl phthalate in humans or animals. A diagram of the metabolic pathway of diethyl phthalate is not provided since so few data were available. The following elucidation of the metabolism of diethyl phthalate is based on *in vitro* studies, and the studies cited may not represent the *in vivo* situation either qualitatively or quantitatively.

The first step of metabolism involves hydrolysis to a monoester derivative. This was seen in the *in vitro* metabolism of ^{14}C-diethyl phthalate (5-mmol/L solution) by hepatic and small intestine preparations from a rodent (rat), a nonrodent (ferret), and a nonhuman primate (baboon)JLake et al. 1977). Hepatic postmitochondrial supematant and intestinal preparations from the rat, baboon, and ferret were able to catalyze the hydrolysis of diethyl phthalate to its monoester derivative. Enzyme activity was expressed as micromoles of product formed per hour per gram of liver (μmol/hour/g) or per milligram of intestinal mucosal cell protein (μmol/hour/mg). Quantitative species differences were observed in the hepatic and intestinal studies. In the hepatic studies, diethyl phthalate hydrolase

activity decreased in the following order: baboon (516 μmol/hour/g) > rat (231 μmol/hour/g) > ferret (45.9 μmol/hour/g). In the intestinal preparation, diethyl phthalate hydrolase activity decreased in the same order: baboon (4.33 μmol/hour/mg) > rat (0.648 μmol/hour/mg) > ferret (0.053 μmol/hour/mg). Studies were also performed with samples of human duodenum and jejunum tissues. As with the three animal species, human intestinal preparations were also active in the metabolism of diethyl phthalate. The results obtained with human intestinal preparations were expressed as nanomoles of product formed per hour per milligram of intestinal protein (nmol/hour/mg). In the human intestinal preparation, the diethyl phthalate hydrolase activity was 31.2-153 nmol/hour/mg in the duodenum and 129 nmol/hour/mg in the jejunum. Similarly, of the tissues from three rat and one human studied *in vitro,* the rat small intestine hydrolyzed the greatest amount (36.4%) of diethyl phthalate in a 16-hour period (Rowland et al. 1977). These results show a qualitative species similarity in the hydrolytic metabolism of diethyl phthalate in humans, a rodent, a nonrodent, and a nonhuman primate.

In both the Lake et al. (1977) and Rowland et al. (1977) studies, attempts were made to identify the products of hydrolysis. In all instances, only one metabolic product was formed that had matching chromatographic properties in thin-layer chromatographic tests using two different solvent systems. These results showed that diethyl phthalate is mono-de-esterified by the liver and intestines. Since diethyl phthalate was hydrolyzed by rat, baboon, ferret, and human intestinal preparations, the investigators suggested that orally ingested diethyl phthalate would most probably be absorbed from the gut of rats, baboons, ferrets, and humans as the corresponding monoester derivative. Any toxic effects of orally ingested diethyl phthalate would more likely be governed by the properties of the corresponding monoester and/or ethanol rather than by intact diethyl phthalate (Lake et al. 1977). The extent of the hydrolysis of diethyl phthalate under *in vivo* conditions, however, has not been established; consequently, the potential effect of intact diethyl phthalate must also be considered.

Although no data were located specifically regarding the complete *in vivo* metabolism of diethyl phthalate, data concerning alkyl phthalic acid esters in general suggest that the extent of hydrolysis depends on the route of administration. Hydrolysis of other phthalate esters is extensive after oral ingestion, but is also dose-related such that, at higher doses, a greater proportion of the intact diester is absorbed (Albro and Laenhar 1989; Pollack et al. 1985). Furthermore, once formed, the monoester

derivative can be further hydrolyzed *in vivo* to phthalic acid and excreted or conjugated to glucuronide and excreted; the terminal or next-to-last carbon atom in the monoester can be oxidized to an alcohol and excreted; or the alcohol can be successively oxidized to an aldehyde, ketone, or carboxylic acid and excreted (Albro and Moore 1974; Albro et al. 1973; EPA 1989; Kluwe 1982).

In another in vitro study, diethyl phthalate inhibited uridine diphosphate glucuronyl transferase (UDPGT) activity of rat liver microsomal preparations (Gollamudi et al. 1985). UDPGT is an important enzyme involved in the Phase II conjugation and detoxication of many endogenous and xenobiotic substances. After incubation of the microsomes for 3 minutes with a 1.35-mmol/L solution of diethyl phthalate, p-nitrophenol-glucuronyl transferase activity was significantly inhibited (33%). Incubation for 6 minutes resulted in 29% inhibition by a 1.35-mmol/L solution of diethyl phthalate. Diethyl phthalate had no effect on rat liver N-acetyltransferase and microsomal cytochrome P-450 in vitro (Gollamudi et al. 1985).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding the excretion of diethyl phthalate or its metabolites by humans or animals following inhalation exposure.

2.3.4.2 Oral Exposure

No studies were located regarding the excretion of diethyl phthalate or its metabolites by humans or animals following oral exposure.

2.3.4.3 Dermal Exposure

No studies were located regarding the excretion of diethyl phthalate or its metabolites by humans following dermal exposure.

Male rats, exposed to a single dermal application of ^{14}C-diethyl phthalate (5-8 mg/cm^2), excreted 24% of the administered dose in the urine and 1% of the dose in feces within 24 hours (Elsisi et al. 1989). Total recovery of the radiolabel in the urine and feces after 7 days was about 50%. No attempt was made to characterize the metabolites found in the urine (Elsisi et al. 1989).

2.3.4.4 Other Routes of Exposure

No studies were located regarding the excretion of diethyl phthalate or its metabolites by humans following exposure by other routes.

^{14}C-diethyl phthalate (2,800 g/kg) was administered intraperitoneally to pregnant rats on either day 5 or day 10 of gestation (Singh et al. 1975). The results showed that radioactivity in the maternal blood increased, reaching a peak during the first 24 hours. The concentration of radioactivity then diminished quickly. A similar pattern was observed in amniotic fluid and fetal tissues. The reduction in concentration of ^{14}C from these tissues as a function of time was found to fit a first-order excretion curve. From this model curve, the half-life was calculated to be 2.22 days for diethyl phthalate. Although the exact chemical nature of the radioactive compounds was not determined, the investigators reported that some of them were probably mixtures of parent compound, monoester, and phthalic acid (Singh et al. 1975).

2.3.5 Mechanisms of Action

No data regarding the absorption or distribution of diethyl phthalate, after oral or inhalation administration, are available, and the results of dermal studies are inadequate to determine a mechanism of action.

2.4 RELEVANCE TO PUBLIC HEALTH

Populations living in areas surrounding hazardous waste sites may be exposed to diethyl phthalate primarily via ingestion of drinking water. Another possible route of exposure is dermal contact with contaminated water. For the general population (i.e., including individuals not living in the vicinity of

hazardous waste sites), most exposure to diethyl phthalate occurs by the use of consumer products containing it; diethyl phthalate is listed as an ingredient in at least 67 cosmetic formulations at concentrations ranging from ≤0.1% to 50%, although most products contain less than 1% diethyl phthalate. The products may be applied to skin, eyes, hair, and nails, and exposure of the mucous membranes and the respiratory tract can occur. Exposure may be frequent (several times a day) or of prolonged duration (years). Exposure can also occur in people receiving medical treatments that involve the use of polyvinyl chloride tubing from which diethyl phthalate can leach. Exposure of the general population can also occur by ingestion of contaminated foods into which diethyl phthalate has leached from packaging materials, ingestion of contaminated seafood, or drinking contaminated water. Occupational exposure to diethyl phthalate can occur in industrial facilities where diethyl phthalate is used in the manufacture of plastics or consumer products.

The liver may be the only target organ of diethyl phthalate exposure. Very mild hepatic effects are observed only after administration of extremely high doses. Otherwise, the only effects reported in animals after acute- and intermediate-duration oral exposure to this compound were death (acute exposure only), decreases in body weight gain, and organ weight changes that were not accompanied by any biochemical, functional, or histopathological evidence of organ injury. Diethyl phthalate is a mild skin irritant in animals and has been reported to cause minimal ocular irritation. In a twogeneration continuous breeding dietary study in mice, the only effect observed other than a decrease in body weight gain was a reduction in the number of live fetuses born to F, parents. Data on the effects of diethyl phthalate following parenteral administration to experimental animals do not provide any additional indication of the target organs of toxicity for this compound. While skeletal abnormalities (primarily elongated and fused ribs, abnormal or incomplete skull bones, and incomplete or missing tail bones) and increased resorptions were observed following intraperitoneal administration of high doses of diethylphthalate to pregnant rats, no such effects were observed in mice administered the compound orally during gestation. No data are available on the carcinogenicity of diethyl phthalate, and *in vitro* genotoxicity studies gave equivocal, although mostly negative, results.

In vitro studies suggest that diethyl phthalate inhibits mitochondrial respiration in hepatic microsomes by interfering with electron transfer (Haubenstricker et al. 1990; Inouye et al. 1978). While this

finding provides a possible mechanism of action for toxic effects of diethyl phthalate, no functional evidence of mitochondrial impairment have been noted in *in vivo* studies.

Minimal Risk Levels for Diethyl Phthalate

Inhalation

No inhalation MRLs were derived for diethyl phthalate. The only known inhalation study in either humans or animals was conducted in an occupational cohort exposed to vapors from organic solvents and welding fumes of cellulose acetate, which contained 30% diethyl phthalate (Beving et al. 1990). This study was limited because of the small cohort size, co-exposure to other contaminants, inappropriate control data, and little exposure information.

Oral

- An MRL of 7 mg/kg/day has been derived for acute oral exposure to diethyl phthalate. This MRL is based on a reproductive study (Jones et al. 1993) in which rats had Leydig cell ultrastructural changes after receiving 2,000 mg/kg/day diethyl phthalate for 2 days by gavage. This result receives support from findings of decreased testosterone concentrations in diethyl phthalate-treated male rats (Oishi and Hiraga 1980). Furthermore, other investigators (Field et al. 1993) derived a developmental NOAEL of 1,910 mg/kg/day in rats. The acute oral MRL is based on the LOAEL of 2,000 mg/kg/day, divided by an uncertainty factor of 300 (3 for the conversion of a minimal LOAEL to a NOAEL, 10 for interspecies extrapolation, and 10 for the protection of sensitive humans).

- An MRL of 6 mg/kg/day has been derived for intermediate-duration oral exposure to diethyl phthalate. This value is based on a minimal LOAEL of 1,753 mg/kg/day for peroxisomal proliferation, slightly elevated liver weight, and changes in hepatic enzyme activities in male rats (Moody and Reddy 1978). The study receives support from a 13-week mouse dietary study in

which the dose equivalent of 1,625 mg/kg/day was the highest NOAEL for body weight gain deficits (Lamb et al. 1987). The LOAEL was divided by an uncertainty factor of 300 (3 for the conversion of a minimal LOAEL to a NOAEL, 10 for interspecies extrapolation, and 10 for interindividual variation) to arrive at the MRL.

The database was not adequate for determination of a chronic oral MRL for diethyl phthalate.

Death. No studies were located regarding death in humans after exposure to diethyl phthalate. Minimal lethal doses of diethyl phthalate have been estimated for several species of experimental animals following both oral and parenteral administration. These doses range from 1,000 to 4,000 mg/kg (intraperitoneal administration) in rats, rabbits, guinea pigs, and mice and from 4,000 to 5,000 mg/kg (oral administration) in rabbits and guinea pigs (Smyth and Smyth 1931). LD_{50} data were available only for parenteral routes of exposure; the intraperitoneal LD_{50} has been reported to range from 2,830 mg/kg in the mouse (Calley et al. 1966) to 8,324 mg/kg in the rat (Singh et al. 1971, 1972, 1973).

Although available information is insufficient to determine whether exposure to diethyl phthalate in the vicinity of hazardous waste sites could produce death in humans, its widespread use in cosmetic formulations without apparent adverse effects and its virtual lack of toxic effects in animal studies suggest that it is not likely to be associated with death at the levels present in the vicinity of hazardous waste sites.

Systemic Effects

Respiratory Effects. No studies were located regarding respiratory effects in humans or animals following inhalation exposure to diethyl phthalate or in humans following oral or dermal exposure to diethyl phthalate. The results of oral and dermal studies in laboratory animals suggest that the respiratory system is not a target tissue after high dose administration of diethyl phthalate (Brown et al. 1978; NTP 1993 [board draft]).

A transient 71% decrease in respiratory rate was observed in rabbits administered a total intravenous dose of 100 mg/kg diethyl phthalate over a 2-3-minute period (Calley et al. 1966). Respiratory rate returned to baseline within 5 minutes. The mechanism for this effect on respiratory rate is not known. This effect should not be considered relevant to human exposure situations because diethyl phthalate was administered in a bolus intravenous injection, which is not an anticipated human exposure.

Histopathological evaluation revealed no evidence of irritation in the lungs of mice given a single intraperitoneal injection of 2,464 mg/kg diethyl phthalate (Lawrence et al. 1975), or any histopathological changes in the lungs of rodents dermally administered up to 300 μL daily in a chronic study (NTP 1993 [board draft]). No change in lung weight was noted in mice administered 125 mg/kg diethyl phthalate by daily intraperitoneal injection for 6 weeks (Calley et al. 1966). Effects seen after parenteral administration may not be relevant to human exposure.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans or animals following inhalation exposure to diethyl phthalate or in humans following oral or dermal exposure to diethyl phthalate. The results of oral and dermal studies in laboratory animals suggest that the cardiovascular system is not a target tissue after high dose administration of diethyl phthalate (Brown et al. 1978; NTP 1993 [board draft]).

A transient 22% decrease in blood pressure was observed in rabbits administered a total intravenous dose of 100 mg/kg diethyl phthalate over a 2-3-minute period (Calley et al. 1966). Blood pressure gradually returned to baseline levels. The mechanism for this effect on blood pressure is not known. This effect should not be considered relevant to human exposure situations because diethyl phthalate was administered in a bolus intravenous injection, which is not an anticipated human exposure route.

Histopathological evaluation revealed no evidence of treatment-related effects in the hearts of mice given a single intraperitoneal injection of 2,464 mg/kg diethyl phthalate (Lawrence et al. 1975), or any histopathological changes in the hearts of rodents dermally administered up to 300 μL daily in a chronic board draft study (NTP 1993). No change in heart weight was noted in mice administered 125 mg/kg diethyl phthalate by daily intraperitoneal injection for 6 weeks (Calley et al. 1966).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans or animals following inhalation exposure to diethyl phthalate or in humans following oral or dermal exposure to diethyl phthalate. Although high dietary concentrations have been associated with enlarged gastrointestinal organs in rats following oral exposure to diethyl phthalate, these effects are apparently not treatment-related (Brown et al. 1978).

Histopathological evaluation revealed no evidence of irritation in the bowel or pancreas of mice given a single intraperitoneal injection of 2,464 mg/kg diethyl phthalate (Lawrence et al. 1975), or any histopathological changes in the gastrointestinal tracts of rodents dermally administered up to 300 μL daily in a chronic board draft study (NTP 1993).

Hematological Effects. No studies were located regarding hematological effects in humans following inhalation, oral, or dermal exposure to diethyl phthalate.

Limited information available from studies in experimental animals indicates that oral (intermediate-duration), dermal (chronic), or parenteral (single-dose) administration of diethyl phthalate had no effect on any hematological parameters measured (Brown et al. 1978; Lawrence et al. 1975; NTP 1993 [board draft]).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals following inhalation or dermal exposure to diethyl phthalate or in humans following oral exposure to diethyl phthalate. High dietary administration of diethyl phthalate to rats did not affect the histological appearance of skeletal muscle (Brown et al. 1978).

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation, oral, or dermal exposure to diethyl phthalate.

Studies indicate that, while it appears that diethyl phthalate can induce an increase in relative liver weight in experimental animals following oral exposure (Brown et al. 1978; Oishi and Hiraga 1980), the absence of any evidence of treatment-related biochemical, functional, or histopathological changes

in the liver suggests that the increase in liver weight may be an adaptive response rather than a direct toxic effect of diethyl phthalate. Other studies have demonstrated minor changes in liver weight or liver enzyme activity in rats after intermediate-duration oral exposure to diethyl phthalate (Moody and Reddy 1978). Results regarding hepatic peroxisomal proliferation after diethyl phthalate treatment are equivocal (Moody and Reddy 1978; Okita and Okita 1992). No histopathological evidence of hepatic irritation or damage has been found after diethyl phthalate administration in mice and rats (Lawrence et al. 1975; NTP 1993 [board draft]).

Renal Effects. No studies were located regarding renal effects in humans after inhalation, oral, or dermal exposure to diethyl phthalate.

Studies indicate that, while it appears that diethyl phthalate can induce an increase in relative kidney weight in experimental animals following oral exposure (Brown et al. 1978), the absence of any reliable evidence of treatment-related biochemical, functional, or histopathological changes in the kidney suggests that the increase in kidney weight may not be a direct toxic effect of diethyl phthalate.

Endocrine Effects. No studies were located regarding endocrine effects in humans or animals following inhalation or dermal exposure to diethyl phthalate or in humans following oral exposure to diethyl phthalate. Dietary administration of high diethyl phthalate concentrations had no effect on the histopathology of the adrenals, pancreas, thyroid, parathyroid, and/or pituitary of laboratory rodents (Brown et al. 1978).

Dermal Effects. No studies were located regarding dermal effects in humans or animals following inhalation or oral exposure to diethyl phthalate or in humans following dermal exposure to diethyl phthalate.

Diethyl phthalate was shown to be very slightly or slightly irritating when applied repeatedly to the intact or abraded skin, respectively, of an unidentified species (Dow Chemical 1952). In rats treated dermally with diethyl phthalate for 2 years, a mild, apparently adaptive skin acanthosis was found

(NTP 1993 [board draft]). Dermal irritancy from diethyl phthalate should not be a concern near hazardous waste sites.

Ocular Effects. No studies were located regarding ocular effects in humans or animals following inhalation exposure to diethyl phthalate or in humans following oral or dermal exposure to diethyl phthalate. Administration of up to 5% dietary diethyl phthalate had no effect on the histology of the eye (Brown et al. 1978), and ocular irritation tests conducted in rabbits indicate that diethyl phthalate is not a primary ocular irritant (Dear and Jassup 1978; Lawrence et al. 1975).

Body Weight Effects. No studies were located regarding body weight effects in humans or animals following inhalation exposure to diethyl phthalate or in humans following oral or dermal exposure to diethyl phthalate. A variety of data from laboratory animal studies indicates body weight gain decrement at doses far in excess of those expected at hazardous waste sites (Brown et al. 1978; Lamb et al. 1987; NTP 1984, 1993 [board draft]). The available data suggest that the effects are primarily attributable to the stress associated with the dosing level rather than to a direct toxic action.

Although available information is insufficient to determine whether exposure to diethyl phthalate in the vicinity of hazardous waste sites could produce systemic toxicity in humans, its widespread use in cosmetic formulations without apparent adverse effects and its virtual lack of toxic effects in animal studies suggest that it is not likely to be associated with systemic effects at the levels present in the vicinity of hazardous waste sites.

Immunological and Lymphoreticular Effects. A patch test study for allergic contact dermatitis was conducted with workers in a factory that produced shoes from polyvinyl chloride granulate (which contains dioctyl-phthalate) (Vidovic and Kansky 1985). One of 30 workers with dermatitis and 1 of 30 without dermatitis responded positively to diethyl phthalate. None of the controls had a positive response. The authors concluded that these results indicate that the phthalates are sensitizers, and that the positive reaction to diethyl phthalate was most likely due to cross-sensitization with dioctyl phthalate since diethyl phthalate is present in very small amounts in polyvinyl chloride.

2. HEALTH EFFECTS

Although the available information is insufficient to determine whether exposure to diethyl phthalate at levels present in the vicinity of hazardous waste sites could induce adverse immunological effects in humans, its widespread use in cosmetic formulations without apparent adverse effect suggests that this is not likely.

Neurological Effects. No studies were located regarding neurological effects in humans or animals following inhalation exposure to diethyl phthalate or in humans following oral or dermal exposure. Oral or dermal administration of high doses had no effect on the histopathological appearance of nervous tissue (Brown et al. 1978; NTP 1993).

Acute-duration parenteral administration studies in mice indicate that diethyl phthalate affected pentobarbital-induced sleep (Calley et al. 1966; Lawrence et al. 1975). This effect may be due to a direct action of diethyl phthalate on the central nervous system or an effect on the hepatic enzymes that metabolize pentobarbital. Neither study had been designed to assess the potential neurotoxicity of diethyl phthalate.

Although the available information is insufficient to determine whether exposure to diethyl phthalate at the levels present in the vicinity of hazardous waste sites could induce adverse neurotoxic effects in humans, its widespread use in cosmetic formulations without apparent adverse effect suggests that this is not likely.

Reproductive Effects. No *in vivo* studies were located regarding reproductive effects in humans following exposure to diethyl phthalate. In vitro, diethyl phthalate adversely affected measures of human sperm motility (Fredricsson et al. 1993). The relationship of the exposure concentrations used in this study to expected concentrations resulting from environmental or occupational exposure is unknown.

In a continuous breeding study in CD-l mice, dietary administration of diethyl phthalate produced physiological effects in F_1 parental animals and significantly decreased their litter size (Lamb et al. 1987). No adverse effects on the physiology, fertility, or reproductive performance of the F_0

generation animals were observed. The parental toxicity in the F_1 generation was evident from a significant decrease in body weight, increased prostate weight in males, and increased liver and pituitary weights in females. However, histological findings in the liver and pituitary were not reported, rendering the toxicological significance of a change in these organ weights unknown. Although a significant decrease in sperm concentration occurred in the males, no adverse effect on the fertility was observed. The total number of live pups per litter was significantly lower in the test group compared to the controls.

Several investigators have studied the effects of diethyl phthalate on male reproductive function in rats since other phthalic acid esters have been shown to be toxic to the male reproductive system (ATSDR 1989; Foster et al. 1980, 1983; Gray and Butterworth 1980; Oishi and Hiraga 1980). Testicular and accessory gland weight and histopathology, as well as biochemical parameters of testicular function, were unaffected by the oral administration of diethyl phthalate to male rats at doses up to 1,600 mg/kg/day (Foster et al. 1980, 1983; Gray and Butterworth 1980; Oishi and Hiraga 1980). At 2,000 mg/kg/day, for 2 days, diethyl phthalate produced mitochondrial swelling and smooth endoplasmic reticulum focal dilation and vesiculation in the Leydig cells of rats. These results were not replicated when the primary hydrolysis product, monoethyl phthalate, was tested in Leydig cell culture (Jones et al. 1993). In cultured rat Sertoli cells, diethyl phthalate had no effect on cyclic adenosine monophosphate (AMP) accumulation or basal lactate production (Heindel and Powell 1992).

Although available information is insufficient to determine whether exposure to diethyl phthalate in the vicinity of hazardous waste sites could produce adverse reproductive effects in humans, its widespread use in cosmetic formulations without apparent adverse effects and its virtual lack of toxic effects in animal studies suggest that it is not likely to be associated with reproductive toxicity at levels present in the vicinity of hazardous waste sites.

Developmental Effects. No studies were located regarding developmental effects in humans after exposure to diethyl phthalate.

Maternal rats receiving 3,210 mg/kg/day of diethyl phthalate throughout organogenesis produced offspring with an increased incidence of skeletal variations, particularly supernumerary ribs. This finding was accompanied by decreased weight gain and decreased food and water consumption in the dams. Exposure to this level or lower dietary concentrations resulted in no additional developmental effects (Field et al. 1993). The significance of the increased incidence of skeletal variations is highly questionable because it occurred only at a dietary concentration associated with maternal effects.

After oral administration of diethyl phthalate to mice (4,500 mg/kg/day on gestation days 6-13), there was no significant evidence of maternal toxicity or neonatal developmental effects in a short-term *in vivo* developmental toxicity screen (Hardin et al. 1987). Developmental toxicity did occur in developing rat embryos when the mother was injected intraperitoneally with diethyl phthalate at doses of 2,884, 5,667, or 9,442 mg/kg/day on days 5, 10, and 15 of gestation (Singh et al. 1971, 1972, 1973). Adverse fetal effects included an increase in the number of skeletal abnormalities and resorption sites. No gross (external) malformations or fetal deaths were seen. Fetal weights were significantly reduced ($p<0.01$). The relevance of these findings with regard to potential developmental toxicity in humans exposed to diethyl phthalate in the vicinity of hazardous waste sites is not known; however, the route of exposure used in this animal study is unlikely to occur in humans.

Genotoxic Effects. No *in vivo* studies were located regarding genotoxic effects in humans or animals following exposure to diethyl phthalate. Data from *in vitro* studies using prokaryotic and cultured mammalian cells are presented in Table 2-3.

A comparison of the results of *in vitro* mutagenic assays of diethyl phthalate in various strains of *Salmonella typhimurium* shows contradictory findings. Diethyl phthalate has been shown to be mutagenic for *L typhimurium* strains TA98, TAl00, and TA1535 mostly without metabolic activation (Agarwal et al. 1985; De Marini et al. 1987; Kozumbo et al. 1982). Contrary to these findings, diethyl phthalate has been found to be nonmutagenic in *S. typhimurium* strains TA98, Tal00, TA1535, TA1537, and TA2637 with or without metabolic activation (Agarwal et al. 1985; DeMarini et al. 1987; NTP 1993 [board draft]; Zeiger et al. 1982, 1985).

TABLE 2-3. Genotoxicity of Diethyl Phthalate *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Ames test *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Zeiger et al. 1982, 1985
8-Azaguanine resistance assay *S. typhimurium* (TA100)	Gene mutation	–	+	Seed 1982
Ames test *S. typhimurium* (TA98, TA100)	Gene mutation	–	+	Kozumbo et. al. 1982
Ames test *S. typhimurium* (TA100, TA1535)	Gene mutation	–	+	Agarwal et. al. 1985
(TA98, TA1537, TA2637)	Gene mutation	–	–	
Ames test *S. typhimurium*[1]				
(TA98)	Gene mutation	+	+	De Marini et. al. 1987
(TA100)	Gene mutation	–	–	
Ames test *S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)	Gene mutation	–	–	Blevins and Taylor 1982
Ames test *S. typhimurium* (TA98, TA100, TA1535, TA1537,	Gene mutation	–	–	NTP 1993
Eukaryotic organisms:				
Mammalian cells:				
Chinese hamster fibroblasts	Chromosomal aberration	–	NA	Ishidate and Odashima 1977
Chinese hamster ovaries	Sister chromatid exchange	+	-	NTP 1993
Chinese hamster ovaries	Chromosomal aberration	-	-	NTP 1993

– = negative result; + = positive result; NA = not applicable to mammalian cell cultures

[1]This test was conducted on a crude solid waste extract.

A well-conducted study investigated the mutagenicity of diethyl phthalate in concentrations ranging from 10 to 10,000 μg/plate in a preincubation modification of the Ames test with and without exogenous metabolic activation using Aroclor 1254-induced rat liver S9 (Zeiger et al. 1982, 1985). The findings indicated that diethyl phthalate was not mutagenic in *S. typhimurium* strains TA1535, TA1537, TA98, or TAl00 with or without metabolic activation. Another Ames test study indicated that diethyl phthalate at 1,000 μg/plate was mutagenic in *S. typhimurium* strain TAl00 but only in the absence of activation (Kozumbo et al. 1982). However, the results are not convincing because the background reversion frequency was too high (291±20) and because the highest response observed for the number of revertants/plate (1.90 ±0.09) was a less than twofold increase. An Ames spot test study indicated that a 50-μg dose of diethyl phthalate did not produce mutagenic results with or without metabolic activation (Blevins and Taylor 1982). The spot test has the limitation of being a qualitative test; a plate incorporation assay should have been conducted before an evaluation of mutagenicity was made. An Ames test study using concentrations of diethyl phthalate ranging from 10 to 2,000 μg/plate showed mutagenicity at 1,500 μg/plate (Agarwal et al. 1985). A threefold increase in the number of revertant colonies was seen in TAl00 without activation, and an approximate twofold increase was seen in TA1535 without activation. An Ames test study examining concentration-response effects in crude wastes and waste extracts containing diethyl phthalate showed a twofold or greater increase in mutagenicity with and without activation in TA98 at a dose (100 μg) much lower than those of other studies suggesting that other impurities may have been present (De Marini et al. 1987). The results of an 8-azaguanine resistance assay in *S. typhimurium* indicated that diethyl phthalate was positive for mutagenicity (Seed 1982). However, the results failed to be significant with less than a twofold increase in the number of mutants per one million cells at the highest concentration of 3.3 mmol/L.

Two chromosomal aberration assays with Chinese hamster fibroblasts and ovaries, respectively, produced negative mutagenic results for diethyl phthalate at concentrations up to 0.324 mg/mL (Ishidate and Odashima 1977; NTP 1993 [board draft]). However, at culture concentrations of 0.05, 0.167, and 0.5 μg/L, diethyl phthalate produced a concentration-related increase in the number of relative sister chromatid exchanges per chromosome. This effect occurred only in the presence of the S9 fraction from rat liver homogenates (NTP 1993 board draft]).

In summary, the results of *in vitro* mutagenicity tests in microbial assays are equivocal. No *in vivo* studies were located. Further studies are required before the genotoxic potential of diethyl phthalate in humans living in the vicinity of diethyl phthalate-contaminated hazardous waste sites can be determined.

Cancer. No studies were located regarding cancer in humans following exposure to diethyl phthalate.

In a recently completed board draft study, dermally applied diethyl phthalate showed no carcinogenic potential in a 2-year rat study and in both initiation and promotion studies in mice. The only evidence for possible carcinogenicity in a 2-year mouse study was an increased incidence of combined hepatic adenomas/carcinomas in both sexes. Growth data suggested that the highest applied dose, 30 μL/day, or 772 mg/kg/day, 5 days/week, was slightly below a maximum tolerated dose (NTP 1993 [board study]). The tumor incidence was dose-related in males only. In general, the results of this study suggest that individuals residing near an NPL site are not at a significant risk of developing cancer from diethyl phthalate exposure.

EPA (IRIS 1994) has classified diethyl phthalate as a Group D chemical--not classifiable as to its carcinogenicity--because pertinent data regarding carcinogenicity were not located in the available literature. Therefore, the carcinogenic potential of diethyl phthalate for humans exposed in the vicinity of hazardous waste sites cannot be determined at this time.

2.5 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).

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 biologic 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 diethyl phthalate are discussed in Section 2.5.1.

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 often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by diethyl phthalate are discussed in Section 2.5.2.

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, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "Populations That Are Unusually Susceptible."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Diethyl Phthalate

Diethyl phthalate can be detected and quantified in human semen and in animal fat and tissues (Giam and Chan 1976; van Lierop and van Veen 1988; Waliszewski and Szymczymski 1990). Limited data

are available regarding the metabolism of diethyl phthalate. An *in vitro* study revealed that the first step of diethyl phthalate metabolism involves hydrolysis to its monoester derivative, monoethyl phthalate (Lake et al. 1977). However, no data are available regarding the identification of this metabolite in the urine, blood, or tissues. In one study, radiolabeled diethyl phthalate was dermally applied to rats (Elsisi et al. 1989). The radiolabel was recovered in the urine; however, no attempt was made to characterize the metabolites found in the urine. Since the monoester derivative of diethyl phthalate is a probable urinary metabolite (although not identified), it could be a useful biomarker of exposure. There are no other known biomarkers of exposure to diethyl phthalate.

2.5.2 Biomarkers Used to Characterize Effects Caused by Diethyl Phthalate

No biomarkers of effects caused by diethyl phthalate have been identified in humans or animals.

2.6 INTERACTIONS WITH OTHER CHEMICALS

No studies have been identified that investigated the effects of exposure to diethyl phthalate together with other chemicals.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to diethyl phthalate than will most persons exposed to the same level of diethyl phthalate in the environment. Reasons include genetic make-up, developmental stage, health and nutritional status, and chemical exposure history. These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or the pre-existing compromised function of target organs. For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, “Populations With Potentially High Exposure.”

Offspring of mice exposed to diethyl phthalate exhibited adverse effects as adults (decreased body weight, increased prostate weight, and decreased sperm count in males; increased liver and pituitary weights in females) (Lamb et al. 1987). These findings suggest that prenatal exposure to diethyl phthalate may be associated with adverse effects in mature offspring. No other information is available on populations with above-average sensitivity to diethyl phthalate.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to diethyl phthalate. 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 diethyl phthalate. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Following dermal exposure to diethyl phthalate, it has been recommended that the skin be immediately washed with copious amounts of soapy water (Stutz and Janusz 1988). If the eyes are exposed to the liquid or vapor, it has been suggested that they be thoroughly flushed with water. Following ingestion of diethyl phthalate, administration of milk, a dilutant and demulcent, has been recommended. Water can be used as an alternative to milk (Haddad and Winchester 1990; Stutz and Janusz 1988). Administration of activated charcoal as an absorptive surface for the contaminant has also been recommended. If ingestion of large amounts of diethyl phthalate has occurred, the administration of a cathartic, such as magnesium sulfate, has been shown to increase the elimination of the substance from the gastrointestinal tract.

2.8.1 Reducing Peak Absorption Following Exposure

Diethyl phthalate is noncorrosive to tissues. Consequently, removal from the gastrointestinal tract either by syrup of Ipecac or by activated charcoal may be possible. These two techniques are effective for approximately 4 to 6-$^{1}/_{2}$ hours after administration, respectively (Ellenhorn and Barceloux 1988). However, because diethyl phthalate has shown little if any toxicological potential, issues regarding reduction in peak absorption may be superfluous.

2.8.2 Reducing Body Burden

Few toxicokinetic data are available on diethyl phthalate. However, even at extremely high exposure concentrations, diethyl phthalate does not have the same toxicological properties as its probable hydrolysis product, ethanol. Because of its apparent negligible toxicity, it is unlikely that body burdens would ever reach levels of concern.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

Few mechanistic data are available on diethyl phthalate. However, as diethyl phthalate shows little toxicity in human and animal studies, an understanding of events that interfere with the mechanism of action may not be necessary.

2.9 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 dietbyl phthalate 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 diethyl phthalate.

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 or eliminate 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 may be proposed.

2.9.1 Existing Information on Health Effects of Diethyl Phthalate

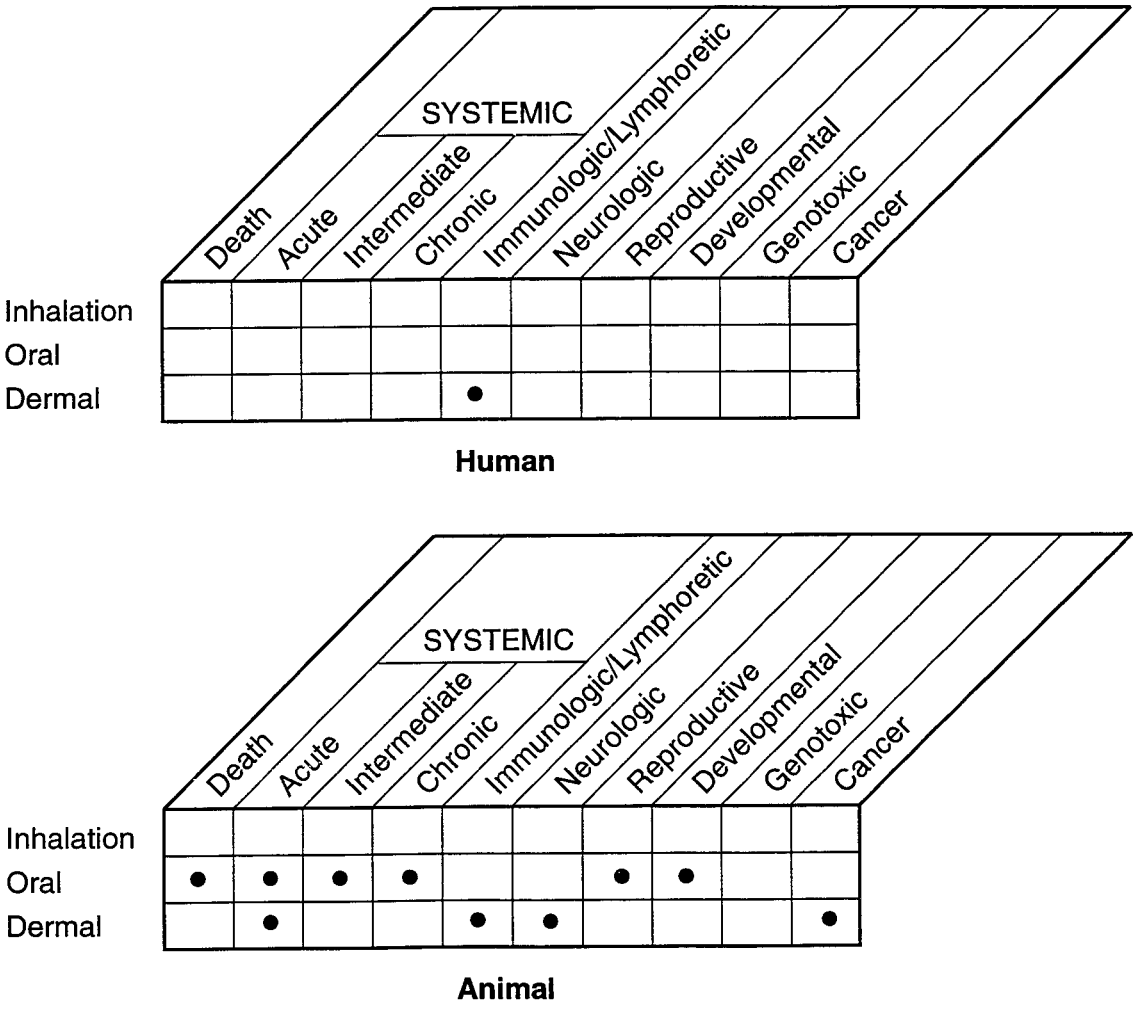
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to diethyl phthalate are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of diethyl phthalate. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As can be seen in Figure 2-2, practically no information is available on the health effects of diethyl phthalate in humans, and very little information is available in animals. Most of the available information on the toxicity of diethyl phthalate in animals comes from studies in which this compound was administered by oral, parenteral (i.e., intraperitoneal, intravenous) or dermal routes. In humans, the only information available is patch test data demonstrating that diethyl phthalate is associated with allergic contact dermatitis in a limited number of polyvinyl chloride workers. Acute oral lethality studies are available in animals. An, acute duration *in vivo* developmental assay and a two-generation reproductive toxicity study were conducted with diethyl phthalate by the oral route. The data avai!able on the effects of dermally administered diethyl phthalate in animals include a board draft report on intermediate duration and chronic exposure studies in rats and mice and additional studies on dermal and ocular irritation.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. There is no information available to identify target organs in humans or animals following acute-duration inhalation or dermal exposure to diethyl phthalate. Although diethyl phthalate has a low vapor pressure ($1.65x10^{-3}$ to $3.45x10^{-4}$ mmHg; Grayson and Fosbraey 1982; Howard et al. 1985) and is relatively nontoxic, airborne vaporization is the major fate process

FIGURE 2-2. Existing Information on Health Effects of Diethyl Phthalate



● Existing Studies

from disposal sites. Consequently, a data need for inhalation studies exists. Minimal lethal oral doses for rabbits and guinea pigs of 4,000-5,000 mg/kg have been reported (Smyth and Smyth 1931), but LD_{50} data are available only for parenteral routes of administration (Galley et al. 1966; Singh et al. 1971, 1972, 1973). A rat study indicated that high dietary levels of diethyl phthalate were associated with ultrastructural testicular changes (Jones et al. 1993). These data were used to calculate an acute-duration oral MRL of 7 mg/kg/day. There are insufficient pharmacokinetic data available to support the extrapolation of results obtained after oral administration to other routes of exposure. However, given findings of minimal toxicity at high oral or dermal doses administered for periods greater than 14 days, additional acute-duration exposure studies seem unnecessary.

Intermediate-Duration Exposure. The only effects seen after a 16-week dietary administration study with diethyl phthalate in rats were a decrease in body weight gain with a concomitant decrease in food consumption (Brown et al. 1978). In 4-week dermal studies with rats and mice, diethyl phthalate produced no observable histopathological changes on any tissue (NTP 1993 [board draft]). Experimental studies (Moody and Reddy 1978; Okita and Okita 1992) indicate that high diethyl phthalate doses have only slight effects on peroxisomal proliferation and have a minor effect on microsomal enzyme induction. The Moody and Reddy (1978) data were used to support an intermediate-duration MRL of 6 mg/kg/day. An inhalation toxicity study would help determine route-specific effects via the potentially most significant exposure route.

Chronic-Duration Exposure and Cancer. No chronic or carcinogenicity studies have been conducted in humans or animals exposed orally or by inhalation. The results of a chronic-duration dermal application study and initiation-promotion experiments indicate that diethyl phthalate has little if any nonneoplastic or neoplastic potential at doses near a Maximum Tolerated Dose (NTP 1993 [board draft]). Although chronic oral data are lacking, the results from the complete database suggest that lifetime exposure near NPL hazardous waste sites would not result in a significant health hazard. A long-term inhalation study to address this issue, in a representative animal species, would help to validate this conclusion.

Genotoxicity. No *in vivo* studies were located regarding genotoxic effects in humans or animals following inhalation, oral, or dermal exposure to diethyl phthalate. The results of in *vitro* mutagenicity tests in microbial systems are equivocal (Agarwal et al. 1985; DeMarini et al. 1987; Kozumbo et al. 1982; NTP 1993 [board draft]; Zeiger et al. 1982, 1985). These studies indicate negative findings for chromosomal aberrations in mammalian cultures, increased sister chromatid exchange frequencies in mammalian cultures, and generally negative incidences of reverse mutation in prokaryotic assays. Given the inconsistent nature of the *in vitro* results, *in vivo* tests of chromosome aberrations in animals exposed to diethyl phthalate would be useful to elucidate the genotoxic potential of this compound.

Reproductive Toxicity. There is no information on the reproductive effects of diethyl phthalate in humans following inhalation, oral, or dermal exposure. This result is consistent with reproductive data from other straight chain-substituted phthalate esters. Diethyl phthalate may produce minor adverse effects on male reproductive organ function or morphology in experimental animals (Jones et al. 1993). In a two-generation continuous breeding dietary reproductive toxicity study in mice, no adverse effect on any measured parameter of fertility was observed in either generation; however, the total number of live pups per litter was significantly lower in litters born to F, parents (Lamb et al. 1987). Oral administration of diethyl phthalate at 2 g/kg body weight in rats resulted in ultrastructural Leydig cell changes, including mitochondrial swelling with focal dilatation of the smooth endoplasmic reticulum (Jones et al. 1993). In the same study, however, *in vitro* Leydig cell testosterone secretion was unaffected by 1 millimolar (mM) monoethyl phthalate treatment. At 0.33 mM and above, diethyl phthalate adversely affected sperm motility (Fredricsson et al. 1993). Monoethyl phthalate at 0.1 mM had no effect on *in vitro* Sertoli cell function (Heindel and Powell 1992). These data confirm and extend the results of previous studies indicating that testicular functional and anatomical changes inconsistently occur at high diethyl phthalate exposure levels. Although few results on female reproductive effects are available, an analysis of the data from both reproductive and developmental studies suggest that no adverse reproductive effects would occur at exposure levels expected near NPL sites. Consequently, no data needs currently exist.

Developmental Toxicity. No information is available on the developmental effects of diethyl phthalate in humans following inhalation, oral, or dermal exposure. No developmental effects were noted in an acute-duration oral *in vivo* developmental toxicity screen in mice (Hardin et al. 1987). An increased incidence of skeletal variations in rat pups, at an oral diethyl phthalate dose of 3,210 mg/kg/day, may have been associated with either a direct toxic effect or with transient maternal malnutrition (Field et al. 1993). However, skeletal abnormalities and an increased number of resorptions were noted following intraperitoneal administration of 3,000-9,000 mg/kg/day diethyl phthalate to pregnant rats (Singh et al. 1971, 1972, 1973). Because of the administration route and the high dose administered, the relevance of this study to human exposure is not known. In general, the data from oral studies, using extremely high exposure conditions, indicate that diethyl phthalate would not be a developmental hazard at occupational or environmental concentrations. Consequently, no data needs currently exist.

Immunotoxicity. Diethyl phthalate may be a contact sensitizer in a limited number of human receptors (Greif 1967; Oliwiecki et al. 1991; Vidovic and Kansky 1985). However, the possibility of cross-sensitization with other compounds, including other phthalate esters, renders the significance of these findings questionable. No reliable animal data were available. A more comprehensive dose-response study using well established sensitized and nonsensitized animal models may help clarify the potential of diethyl phthalate as an immunotoxic agent.

Neurotoxicity. No information is available on the neurological effects of diethyl phthalate in humans or animals following inhalation, oral, or dermal exposure. Acute-duration parenteral administration studies in mice indicate that diethyl phthalate affected pentobarbital-induced sleep (Calley et al. 1966; Lawrence et al. 1975). However, this effect may be due to a direct action of diethyl phthalate on. the central nervous system or an effect on the hepatic enzymes that-metabolize pentobarbital. There currently exists a need for observing overt or histopathological evidence of neurological aberrations in a controlled animal study.

Epidemiological and Human Dosimetry Studies. No epidemiological studies are available on populations that have been exposed solely to diethyl phthalate. As a result of its use, together with other phthalate esters, as a plasticizer for cellulose ester films and in extruded materials and a variety of consumer products (including cosmetics and skin care preparations) (Anonymous 1985; Kamrin and Mayor 1991), exposure of the general population and of workers in occupational settings is significant. Therefore, it is unlikely that both a specific subpopulation exposed only to diethyl phthalate and a control population with no known exposure could be identified. Given this inability to find suitably exposed subpopulations, as well as diethyl phthalate's low systemic toxicity and apparent lack of target organ effects at occupational or environmental concentrations, epidemiological and human dosimetry studies are both unfeasible and unnecessary. A better understanding of the role of the liver as a potential target organ should take precedence.

Biomarkers of Exposure and Effect. Ethanol and phthalic acid, the putative diethyl phthalate hydrolysis products, are nonspecific biomarkers. The pharmacokinetics of the only potential specific biomarker of exposure, monoethyl phthalate, are unknown. Furthermore, no adverse effects specific to diethyl phthalate have been identified. Because of the unlikelihood that the vast proportion of individuals occupationally or environmentally exposed to diethyl phthalate will show any adverse effects, research to find biomarkers of exposure seems unnecessary.

Since exposure to diethyl phthalate does not produce a unique clinical disease state, no biomarkers of effect have been identified.

Absorption, Distribution, Metabolism, and Excretion. No studies were located regarding the absorption of diethyl phthalate following inhalation or oral exposure in humans or animals. No *in vivo* studies were located regarding absorption of diethyl phthalate following dermal exposure-in humans. However, an *in vivo* animal study (Elsisi et al. 1989) and several *in vitro* studies (Hotchkiss et al. 1992; Mint et al. 1992; Scott et al. 1987) indicate that diethyl phthalate is absorbed through the skin of humans and rats. Using the amount of radiolabel present as an index of percutaneous absorption, 24% of a single dose of 34.89 mg/kg applied dermally to rats was excreted in the first 24 hours (Elsisi et al. 1989). A cumulative total of 50% was excreted after 7 days. An in vitro study of the absorption of

diethyl phthalate through human and rat epidermal membranes indicates that diethyl phthalate is slowly absorbed through both human and rat skin; however, diethyl phthalate was absorbed more quickly through rat skin than through human skin. The results showed that rat skin was more permeable to diethyl phthalate than human skin. Following contact with diethyl phthalate, there was an increase in the permeability for both human and rat skin. However, rat skin showed a much greater change in permeability indicating that irreversible alteration of the membrane permeability occurred as a result of exposure to diethyl phthalate (Scott et al. 1987). Additional oral and inhalation *in vivo* absorption data would be useful in order to assess the relative rates and extent of absorption and may help in the identification of potential mechanisms of action.

No studies were located regarding the distribution of diethyl phthalate following inhalation or oral exposure in humans or animals. No studies were located regarding distribution in humans following dermal exposure. Only one study was located regarding distribution in animals following dermal exposure (Elsisi et al. 1989). The results of this acute study in rats showed that although tissue distribution was wide, diethyl phthalate and/or its metabolites are not likely to accumulate in the tissues to any great extent. Less than 5% of the administered dose was found in the tissues (brain, lung, liver, spleen, small intestine, kidney, testis, spinal cord, blood, adipose tissue, muscle, and skin). An acute intraperitoneal study in rats showed that diethyl phthalate crossed the placenta from mother to fetus and was distributed in maternal blood, placenta, amniotic fluid, and fetal tissue; however, very little (<1%) of the dose was present (Singh et al. 1975). Limited additional experimental data for both humans and animals would be useful in order to adequately assess similarities and differences in the distribution of diethyl phthalate and/or its metabolites after oral or inhalation exposure.

Very limited information is available regarding the metabolism of diethyl phthalate (Gollamudi et al. 1985; Lake et al. 1977). In vitro studies indicate that the first step in the metabolism of diethyl phthalate involves hydrolysis to a monoester derivative (Lake et al. 1977). Although data on the metabolism of phthalate diesters as a class were located, more specific data on diethyl phthalate would help to adequately characterize the metabolism of this compound. The significance of high dose effects observed in toxicity studies may be clarified by metabolism findings. For example, properly designed studies would indicate whether metabolic saturation occurs at high doses, which may help

explain the excess metabolic demands that such doses entail. This information may be essential for determining whether an MRL can be derived.

No studies were located for humans or animals regarding the excretion of diethyl phthalate following inhalation or oral exposure. Very limited data indicate that diethyl phthalate is excreted primarily in the urine following acute dermal exposure in rats (Elsisi et al. 1989). An excretion half-life of 2.2 days was calculated for diethyl phthalate in rats (Singh et al. 1975). Dose-response information on the identity of the metabolites excreted would help clarify the significance of high-dose effects, including hepatic peroxisomal proliferation (Moody and Reddy 1978), ultrastructural testicular changes (Jones et al. 1993), and body weight gain inhibition (Lamb et al. 1987).

Comparative Toxicokinetics. Limited in vitro data indicate that both humans and rats absorb diethyl phthalate relatively slowly through the skin but that rats seem to absorb the compound more quickly than humans (Elsisi et al. 1989; Scott et al. 1987). Few data are available to adequately indicate the similarities and/or differences in target organs. Toxicokinetic studies (in vitro) have been performed in both humans and animals (multiple species); however, the data are extremely limited. Humans and animals (rodent, nonrodent, and nonhuman primate) were qualitatively similar in their ability to hydrolyze diethyl phthalate in the intestines and liver. However, quantitative species differences were observed in the rates of hydrolase activity of the rodent, nonrodent, and nonhuman primate with the order being primate > rodent > nonrodent (Lake et al. 1977). Excretion data identifying the metabolites of diethyl phthalate found in the urine and feces of humans and in multiple animal species would be useful in order to adequately assess which animals can serve as the best models.

Methods for Reducing Toxic Effects. All of the treatment methods currently available for use in diethyl phthalate ingestion or skin contact are supportive in nature and/or involve decreasing absorption or hastening elimination of diethyl phthalate (Haddad and Winchester 1990; Stutz and Janusz 1988). Since the mechanism of diethyl phthalate toxicity is not known, there are currently no methods geared towards mitigating the effects of diethyl phthalate by interfering with its mode of action. Therefore, more information on the mechanism of action for diethyl phthalate would be useful

in order to devise methods for the mitigation of any potential toxic effect, such as peroxisomal proliferation.

2.9.3 On-going Studies

No on-going studies on the health effects or toxicokinetics of diethyl phthalate were found.