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 hydraulic fluids. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

As discussed in Chapters 3,4, and 5 of this profile, hydraulic fluids are materials that transmit energy in fluid-filled, pressurized mechanical systems such as automotive automatic transmissions, vehicular brake equipment, power steering equipment, and hydrostatic drive systems used in agricultural, construction, mining, and aircraft equipment and machinery. Hydraulic fluids are defined primarily on an operational basis. Thus, any fluid, regardless of chemical composition, that is used to transmit pressure in a closed system is a hydraulic fluid. Based on chemical and functional properties, hydraulic fluids can be divided into sevenchemical classes: phosphate esters, mineral-oil-in-water and water- in-oil fluids, polyalphaolefin oligomers, polyhalohydrocarbons, polyglycols, silicate esters, and silicones. This profile focuses on three classes of hydraulic fluids: mineral-oil-based hydraulic fluids, polyalphaolefins, and organophosphate esters (Moller 1989; U.S. Air Force 1989; Wills 1980). Some of these fluids have special applications in industry and the military and may be found at hazardous waste sites. Automobile hydraulic fluids (brake, transmission, or power steering fluids) are not specifically addressed in this profile. Some of the specific fluids discussed in this profile are no longer manufactured, but may nonetheless be at hazardous waste sites.

Mineral-oil based hydraulic fluids (including fire-resistant mixtures of mineral oil and water) have been estimated to comprise 98% of the world demand for hydraulic fluids (Wills 1980). These fluids are made from dewaxed petroleum-based crude oils that are blended with additives such as corrosion inhibitors (e.g., fatty acids), oxidation inhibitors (e.g., phenols, amines, and sulfides), defoamers (e.g., silicone oils), and antiwear additives (e:g., organophosphate esters) (FMC 1991c, 1991d, 1992a, 1992b; Moller1989). Thus, mineral-oil-based hydraulic fluids are complex mixtures of aliphatic and aromatic hydrocarbons to which other compounds have been added. The chemical composition of these fluids varies with manufacturer and depends on the source of the crude oil, the degree and type of refining applied to the crude oil, and the amount and types of compounds added for operational purposes. Mineral-oil-based hydraulic fluids are widely used in hydrostatic machines, hydrodynamic couplings, automatic transmissions, and tractors. Hydraulic systems

2. HEALTH EFFECTS

used in situations where combustion is a danger (e.g., underground mining, foundries, and in welding equipment) often contain oil-in-water emulsions (>80% water) or water-in-oil emulsions (>40% water) as fire-resistant hydraulic fluids (Moller 1989).

Organophosphate esters are among the most widely used classes of synthetic compounds in hydraulic fluids. They are used as anti-wear additives in mineral oil hydraulic fluids and are significant components in certain fire-resistant hydraulic fluids (FMC 1991c, 1991 d, 1992a, 1992b; Wills 1980). Organophosphate esters have better fire resistance than mineral oils and are much better lubricants than water. Common types of organophosphate esters include tricresyl phosphates, isopropylated phenyl phosphates, tributyl phosphates, and tertiary butylated phenyl phosphates (Moller 1989; Wills 1980; Henrich 1995). Organophosphate ester hydraulic fluids and additives often contain mixtures of organophosphate esters. The only other synthetic compounds likely to have a wider use in hydraulic fluids are the polyalkylene glycols, which are widely used in the hydraulic brake systems of motor vehicles (Moller 1989; Wills 1980). The toxicological properties of two important polyalkylene glycols are discussed in the ATSDR technical report on ethylene glycol and propylene glycol (ATSDR 1993a). The polyalkylene glycols are not discussed in this profile.

The third class of hydraulic fluids discussed in this profile is the polyalphaolefins. Polyalphaolefins are synthetic hydrocarbons that are made by oligomerizing alphaolefins such as 1 -decene (see Chapters 3,4, and 5). Aliphatic hydrocarbons are the principal components of both mineral oils and polyalphaolefins, but the array of hydrocarbons with differing molecular weights is much narrower in polyalphaolefins than in mineral oils. Certain polyalphaolefins maintain good operational characteristics at low temperatures and have been proposed for use in hydraulic systems in U.S. military aircraft (Kinkead et al. 1992b).

Hydraulic fluids are generally mixtures comprised of major and minor components whose presence may or may not be public information. Adverse health effects from exposure to mixtures can be caused by potent components, which may represent only minor portions of the whole mixture and whose presence may not be common knowledge. In the ensuing discussion of health effects from three classes of hydraulic fluids, attempts were made to identify tested hydraulic fluids by their commercial names and to focus-on what is known about the toxicological properties of the fluids themselves. Available information concerning the known chemical components of hydraulic fluids for which toxicological studies were located is discussed in Chapter 3. Information concerning the toxicological properties of major components expected to be found in hydraulic fluids discussed in this profile is discussed for tricresyl phosphate (TCP) and tributyl phosphate, because they comprise nearly 100% of some organophosphate ester hydraulic fluids (in the past and

currently) and because they have important neurotoxic effects. Other individual components are discussed to a limited extent because of the uncertainty in extrapolating to effects caused by the complete mixture. The toxicity of these complex mixtures depends on interactions of all the components. Some components, when found together, may act additively or synergistically to enhance toxic effects. Other components may be antagonistic in combination, thus diminishing toxic effects. It cannot always be predicted how a mixture will behave based on the toxicity of its individual components. However, the toxic characteristics of the individual components may be an indicator of the potential toxicological responses of the mixture.

A few case studies have reported neurological effects in humans following exposure to hydraulic fluids that probably contained organophosphorus compounds. Animal studies indicate that neurological effects are the most clearly identified health hazard associated with exposure to hydraulic fluids containing organophosphorus compounds. Because organophosphorus compounds are often added to fluids in which mineral oil or polyalphaolefins are the principal components, concern for the development of neurological effects is not restricted to fluids in which organophosphorus compounds are the principal components.

Acute exposure to many organophosphorus compounds can cause at least one of two types of neurological effects: acute inhibition of acetylcholinesterase, an enzyme that controls transmission of nerve impulses at synapses, and organophosphorus-induced delayed neuropathy (OPIDN), a slowly developing axonal degeneration and demyelination in central and peripheral nerve tissues. Symptoms of acetylcholinesterase inhibition develop quickly (within hours of exposure) and include salivation, vomiting, diarrhea, muscle fasciculations, and general paralysis (see Table 2-10). OPIDN symptoms include weakness, ataxia, and paralysis, and are thought to develop through a mechanism distinct from acetylcholinesterase inhibition. Triaryl phosphates, particularly tri-*ortho*-cresyl phosphate (TOCP), are most closely associated with OPlDN, and studies of structure-activity relations of organophosphate esters that produce OPIDN have provided general relationships to predict neuropathy from chemical structure (Johanson 1977; Johnson 1990). It should be noted that chickens, cats, dogs, and ruminants are generally considered to be better models for human OPIDN than are rats, mice, and rabbits (see Section 2.3.5 for more details).

The number of organophosphate esters and similar compounds used in hydraulic fluids is considerable. A core number (approximately 10) have been studied to some degree for toxicity. Though many hydraulic fluids are proprietary mixes of several organophosphate esters as originally formulated, environmental exposure to organophosphate esters is more complex because transformation to chemicals with greater or lesser toxicity than the original product may occur with time. Individual esters and whole hydraulic fluid

2. HEALTH EFFECTS

product toxicity is presented in Sections 2.2 through 2.5, because toxicological research has involved both. Discussions on one closely related chemical, cyclotriphosphazene, are also provided because of structural and functional similarities. TOCP was a component of several triaryl organophosphate ester based hydraulic fluids, but was removed from formulations because of its toxicity. An attempt has been made to deemphasiz TOCP as a hydraulic fluid component, but it is included to illustrate toxicological properties.

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

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

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

2.2.1 Inhalation Exposure

The NOAEL and LOAEL values for each effect after inhalation exposure are shown in Tables 2-1,2-2, and 2-3 and plotted in Figures 2-1,2-2, and 2-3 for mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, and polyalphaolefin hydraulic fluids, respectively.

2.2.1.1 Death

Mineral Oil Hydraulic Fluids. No studies were located regarding death in humans after inhalation exposure to mineral oil hydraulic fluids.

Several water-in-oil emulsion hydraulic fluids (Houghto-Safe 5047F, Sunsafe F, Pyroguard A-443, and Quintolubric 95830W) produced no deaths or clinical signs of toxicity in rats within 14 days of single 4-hour exposures to aerosol concentrations ranging from 110 to 210 mg/m^3 (Kinkead et al. 1987a, 1988). No deaths were reported in Fischer-344 rats during a 90-day continuous exposure (23 hours/day) to 1 .0 mg/m^3

Table 2-1. Levels of Significant Exposure to Mineral Oil Hydraulic Fluids - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m3)	LOAEL		Reference Fluid Identity
					Less serious (mg/m3)	Serious (mg/m3)	
ACUTE EXPOSURE							
Systemic							
1	Rat (Fischer- 344)	4 hr	Bd Wt	210			Kinkead et al. 1987a; Kinkead et al. 1988 Houghto-Safe 5047F
2	Rat (Sprague-Dawley)	6 hr	Bd Wt	1148			Kinkead et al. 1985 MIL-H-5606
3	Rat (Fischer- 344)	4 hr	Bd Wt	110			Kinkead et al. 1987a; Kinkead et al. 1988 Pyroguard A-443
4	Rat (Fischer- 344)	4 hr	Bd Wt	180			Kinkead et al. 1987a; Kinkead et al. 1988 Quintolubric 95830W
5	Rat (Fischer- 344)	4 hr	Bd Wt	180			Kinkead et al. 1987a; Kinkead et al. 1988 Sunsafe F

Table 2-1. Levels of Significant Exposure to Mineral Oil Hydraulic Fluids - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m3)	LOAEL		Reference Fluid Identity
					Less serious (mg/m3)	Serious (mg/m3)	
INTERMEDIATE EXPOSURE							
Systemic							
6	Rat (Fischer- 344)	90 d 23 hr/d	Resp	1.0			Kinkead et al. 1991 Houghto-Safe 5047F
			Cardio	1.0			
			Hepatic	1.0			
			Renal	1.0			
			Bd Wt	1.0			

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

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Resp = respiratory

Figure 2-1. Levels of Significant Exposure to Mineral Oil Hydraulic Fluids - Inhalation

Acute (≤14 days)

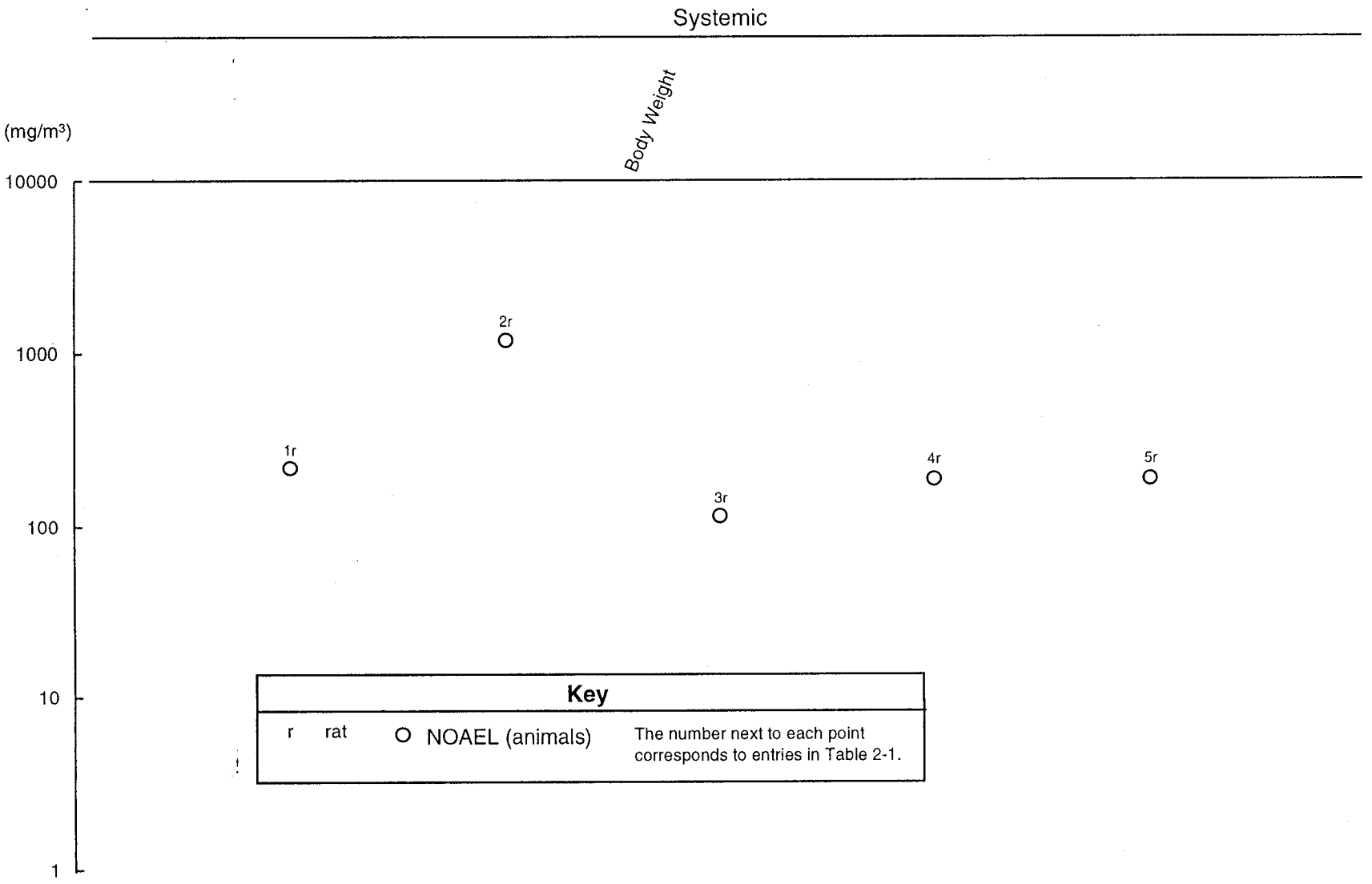


Figure 2-1. Levels of Significant Exposure to Mineral Oil Hydraulic Fluids - Inhalation

Intermediate (15-364) days)

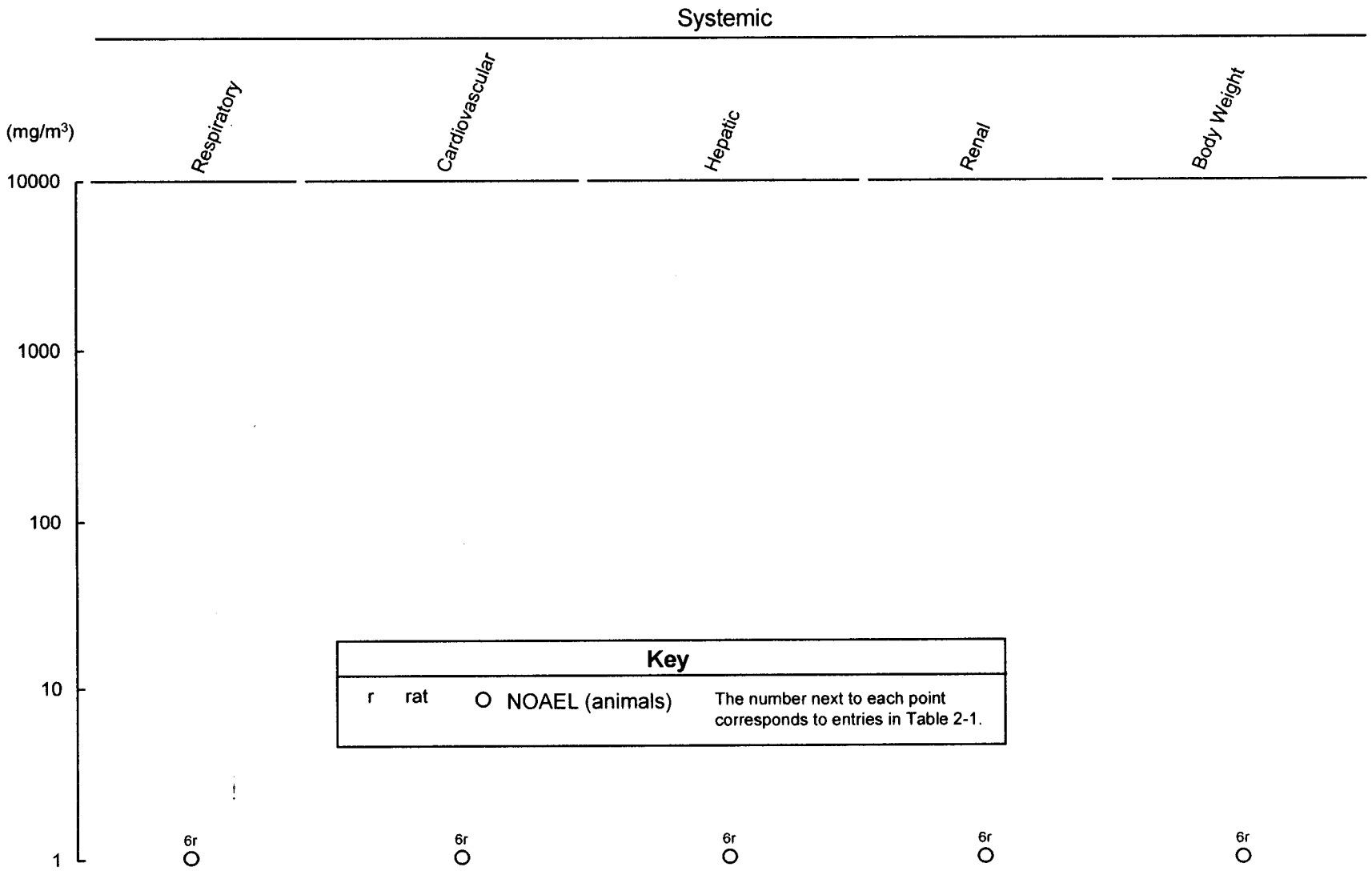


Table 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Inhalation

Key to[a] figure	Species/ (strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Fluid Identity
ACUTE EXPOSURE							
Systemic							
1	Rat (Sprague-Dawley)	4 hr	Resp	6350 F			Gaworski et al. 1986 Durad MP280
			Hepatic	6350 F			
			Renal	6350 F			
			Bd Wt	6350 F			
2	Rat (Sprague-Dawley)	4 hr	Resp	6310 F			Gaworski et al. 1986; Kinkead et al. 1992a Fyrquel 220
			Hepatic	6310 F			
			Renal	6310 F			
			Bd Wt	6310 F			
Neurological							
3	Rat (Sprague-Dawley)	4 hr			6190 (mild lethargy)		Gaworski et al. 1986 Durad MP280
4	Rat (Sprague-Dawley)	4 hr			5790 (mild lethargy)		Gaworski et al. 1986; Kinkead et al. 1992a Fyrquel 220
5	Mouse (Carworth Farms CF-1)	2-6 hr		363 M	757 M (24% decrease in whole blood cholinesterase)		Sutton et al. 1960 TPP

Table 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)		LOAEL Serious (mg/m3)		Reference Fluid Identity
INTERMEDIATE EXPOSURE									
Death									
6	Rabbit (New Zealand)	90 d					101	(8/8 died within 49 days)	MacEwen and Vernot 1983 Durad MP280
7	Rabbit (New Zealand)	90 d					100	(3/8 died)	MacEwen and Vernot 1983 Fyrquel 220
8	Rabbit (New Zealand)	52-163 d					102	(3/3 died)	Siegel et al. 1965 TAP1
Systemic									
9	Monkey (Squirrel)	6 wk 5 d/wk 8 hr/d	Resp	50					Siegel et al. 1965 TAP1
			Cardio	50					
			Hepatic	50					
			Renal	50					
			Bd Wt		25	(11% body weight loss)			
10	Monkey (Squirrel)	108 d	Resp	4.4					Siegel et al. 1965 TAP1
			Cardio	4.4					
			Hepatic	4.4					
			Renal	4.4					

Table 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Fluid Identity
11	Rat (Fischer- 344)	21 d 5 d/wk 6 hr/d	Resp	990			Kinkead et al. 1990; Kinkead et al. 1989a cyclotriphos-phazene
			Cardio	990			
			Gastro	990			
			Hemato	990			
			Musc/skel	990			
			Hepatic	990			
			Renal		240 (hyaline droplet accumulation)		
			Endocr	990			
			Dermal	990			
			Ocular	990			
			Bd Wt	990			
12	Rat (Fischer- 344)	90 d	Resp	101			MacEwen and Vernot 1983 Durad MP 280
			Cardio	101			
			Gastro	101			
			Hepatic	101			
			Hemato	10.3	101 (leukocytosis)		
			Musc/skel	10.3		101 (kyphosis)	
			Renal	101			
			Bd Wt	101			

Table 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Fluid Identity
13	Rat (Fischer- 344)	21 d 5 d/wk 6 hr/d	Resp	251			MacEwen and Vernot 1983; Gaworski et al. 1986 Durad MP 280
			Cardio	251			
			Hemato	251			
			Hepatic	251			
			Renal	251			
			Bd Wt	251			
14	Rat (Fischer- 344)	90 d	Hemato	10.3	101 M (leukocytosis)		MacEwen and Vernot 1983 Durad MP280
			Musc/skel	10.3	101 (kyphosis)		
15	Rat (Fischer- 344)	90 d	Resp	100			MacEwen and Vernot 1983 Fyrquel 220
			Cardio	100			
			Gastro	100			
			Hemato	100			
			Musc/skel	10.1		100 (kyphosis)	
			Hepatic	100			
			Renal	100			
			Endocr	100			
			Dermal	100			
			Bd Wt	100			
16	Rat (Fischer- 344)	21 d 5 d/wk 6 hr/d	Resp	260			MacEwen and Vernot 1983; Gaworski et al. 1986 Fyrquel 220
			Cardio	260			
			Hemato	260			
			Hepatic	260			
			Bd Wt	260			

Table 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Fluid Identity
17	Rat (Crl:CD (SD)BR)	6 or 13 wk 5 d/wk 6 hr/d	Resp	5.3	100 (nasal discharge)		Healy et al. 1992; Monsanto 1987a, 1987b, 1989 Skydrol 500B-4
			Cardio	300			
			Gastro	300			
			Hemato	100	300 (decreased RBC, hematocrit, hemoglobin levels)		
			Musc/skel	300			
			Hepatic	100	300 (mild hepatocellular vacuolation and increased liver weight)		
			Renal	300			
			Endocr	300			
			Ocular	300			
			Dermal	300			
			Bd Wt	300			
18	Rat (Long- Evans)	36-163 d	Resp	110			Siegel et al. 1965 TAP1
			Cardio	110			
			Hepatic	110			
			Renal	110			
19	Hamster (Golden)	90 d	Resp	101 M			MacEwen and Vernot 1983 Durad MP280
			Cardio	101 M			
			Gastro	101 M			
			Hepatic	101 M			
			Renal	101 M			
			Endocr	101 M			
			Dermal	101 M			
			Bd Wt	101 M			

Table 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Fluid Identity
20	Hamster (Golden Syrian)	21 d 5 d/wk 6 hr/d	Resp	251 M			MacEwen and Vernot 1983; Gaworski et al. 1986 Durad MP280
			Cardio	251 M			
			Hepatic	251 M			
			Renal	251 M			
			Endocr	251 M			
			Bd Wt	251 M			
21	Hamster (Golden)	90 d	Resp	100 M			MacEwen and Vernot 1983 Fyrquel 220
			Cardio	100 M			
			Gastro	100 M			
			Hepatic	100 M			
			Renal	100 M			
			Endocr	100 M			
			Dermal	100 M			
			Bd Wt	100 M			
22	Hamster (Golden Syrian)	21 d 5 d/wk 6 hr/d	Resp	260 M			MacEwen and Vernot 1983; Gaworski et al. 1986 Fyrquel 220
			Cardio	260 M			
			Hepatic	260 M			
			Renal	260 M			
			Bd Wt	260 M			
23	Dog (Beagle)	30 d 8 hr/d 5 d/wk	Resp	50			Siegel et al. 1965 TAP1
			Cardio	50			
			Hepatic	50			
			Renal	50			
			Bd Wt	25	50 (1-10% loss of body weight)		

Table 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Fluid Identity
24	Dog (Beagle)	36-136 d	Resp	103			Siegel et al. 1965 TAP1
			Cardio	103			
			Hepatic	103			
			Renal	103			
25	Rabbit (New Zealand)	90 d	Resp	101			MacEwen and Vernot 1983 Durad MP280
			Cardio	101			
			Gastro	101			
			Hepatic	101			
			Renal	101			
			Endocr	101			
			Dermal	101			
26	Rabbit (New Zealand)	21 d 5 d/wk 6 hr/d	Resp	251			MacEwen and Vernot 1983; Gaworski et al. 1986 Durad MP280
			Cardio	251			
			Hemato	251			
			Hepatic	251			
			Renal	251			
			Endocr	251			
			Bd Wt	251			

Table 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Fluid Identity
27	Rabbit (New Zealand)	90 d	Resp	100			MacEwen and Vernot 1983 Fyrquel 220
			Cardio	100			
			Gastro	100			
			Hepatic	100			
			Renal	100			
			Endocr	100			
			Dermal	100			
28	Rabbit (New Zealand)	21 d 5 d/wk 6 hr/d	Resp	260			MacEwen and Vernot 1983; Gaworski et al. 1986 Fyrquel 220
			Cardio	260			
			Gastro		26 (transient diarrhea)		
			Hemato	260			
			Hepatic	260			
			Renal	260			
			Bd Wt	260			
Immunological/Lymphoreticular							
29	Rat (Fischer- 344)	21 d 5 d/wk 6 hr/d		990			Kinkead et al. 1990; Kinkead et al. 1989a cyclotriphosphazene
30	Rat (Fischer- 344)	21 d 5 d/wk 6 hr/d		251			MacEwen and Vernot 1983; Gaworski et al. 1986 Durad MP280
31	Rat (Fischer- 344)	21 d 5 d/wk 6 hr/d		260			MacEwen and Vernot 1983; Gaworski et al. 1986 Fyrquel 220

Table 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Fluid Identity
32	Rat (Crl:CD (SD)BR)	6 or 13 wk 5 d/wk 6 hr/d		300			Healy et al. 1992; Monsanto 1987a, 1987b, 1989 Skydrol 500B-4
33	Hamster (Golden Syrian)	21 d 5 d/wk 6 hr/d		251 M			MacEwen and Vernot 1983; Gaworski et al. 1986 Durad MP280
34	Hamster (Golden)	90 d		100 M			MacEwen and Vernot 1983 Fyrquel 220
35	Hamster (Golden Syrian)	21 d 5 d/wk 6 hr/d		260 M			MacEwen and Vernot 1983; Gaworski et al. 1986 Fyrquel 220
36	Rabbit (New Zealand)	90 d		101			MacEwen and Vernot 1983 Durad MP280
37	Rabbit (New Zealand)	21 d 5 d/wk 6 hr/d		251			MacEwen and Vernot 1983; Gaworski et al. 1986 Durad MP280
38	Rabbit (New Zealand)	90 d		100			MacEwen and Vernot 1983 Fyrquel 220
39	Rabbit (New Zealand)	21 d 5 d/wk 6 hr/d		260			MacEwen and Vernot 1983; Gaworski et al. 1986 Fyrquel 220

Table 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Fluid Identity
	Neurological						
40	Monkey (Squirrel)	108 d		4.4			Siegel et al. 1965 TAP1
41	Monkey (Squirrel)	30 x 5 d/wk 8 hr/d		50			Siegel et al. 1965 TAP1
42	Rat (Fischer- 344)	21 d 5 d/wk 6 hr/d		990			Kinkead et al 1990; Kinkead et al. 1989a cyclotriphosphazene
43	Rat (Fischer- 344)	90 d		10.3		101 M (kyphosis; decline in tail tip curl)	MacEwen and Vernot 1983 Durad MP280
44	Rat (Fischer- 344)	90 d		10.1		100 (kyphosis, decline in tail tip curl)	MacEwen and Vernot 1983 Fyrquel 220
45	Rat (Crl:CD (SD)BR)	6 or 13 wk 5 d/wk 6 hr/d		100	300 (excessive salivation)		Healy et al. 1992; Monsanto 1987a, 1987b, 1989 Skydrol 500B-4
46	Rat (Long- Evans)	36-163 d continuous		110			Siegel et al. 1965 TAP1
47	Hamster (Golden)	90 d		101 M			MacEwen and Vernot 1983 Durad MP280
48	Hamster (Golden)	90 d		100 M			MacEwen and Vernot 1983 Fyrquel 220
49	Dog (Beagle)	36-163 d		103			Siegel et al. 1965 TAP1

Table 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)		Reference Fluid Identity
50	Rabbit (New Zealand)	90 d		10.3		101	(cachexia, head droop, anorexia, and lethargy)	MacEwen and Vernot 1983 Durad MP280
51	Rabbit (New Zealand)	90 d		100				MacEwen and Vernot 1983 Fyrquel 220
52	Rabbit (New Zealand)	52-163 d		34		102	(hind limb paralysis in 3/3 rabbits)	Siegel et al. 1965 TAP1
53	Chicken (White Vantress)	36-163 d		4.4 F		23 F	(severe delayed neuropathy in 2/7 hens)	Siegel et al. 1965 TAP1
	Reproductive							
54	Rat (Fischer- 344)	21 d 5 d/wk 5 hr/d		990				Kinkead et al. 1990; Kinkead et al. 1989a cyclotriphosphazene
55	Rat (Fischer- 344)	90 d		10.3		101 M	(testicular atrophy)	MacEwen and Vernot 1983 Durad MP280
56	Rat (Fischer- 344)	90 d		100				MacEwen and Vernot 1983 Fyrquel 220
57	Rat (Crl:CD(SD) BR)	13 wk 5 d/wk 6 hr/d		300				Healy et al. 1992; Monsanto 1987a, 1987b, 1989 Skydrol 500B-4

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

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; exp. = exposure(s); F = female; Gastro = gastrointestinal; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; RBC = red blood cell; Resp = respiratory; TAP1 = triaryl phosphate hydraulic fluid (TAP1 is similar, if not identical, to Cellulube 220); TPP = triphenyl phosphate; wk = week(s); x = times.

Figure 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids Inhalation

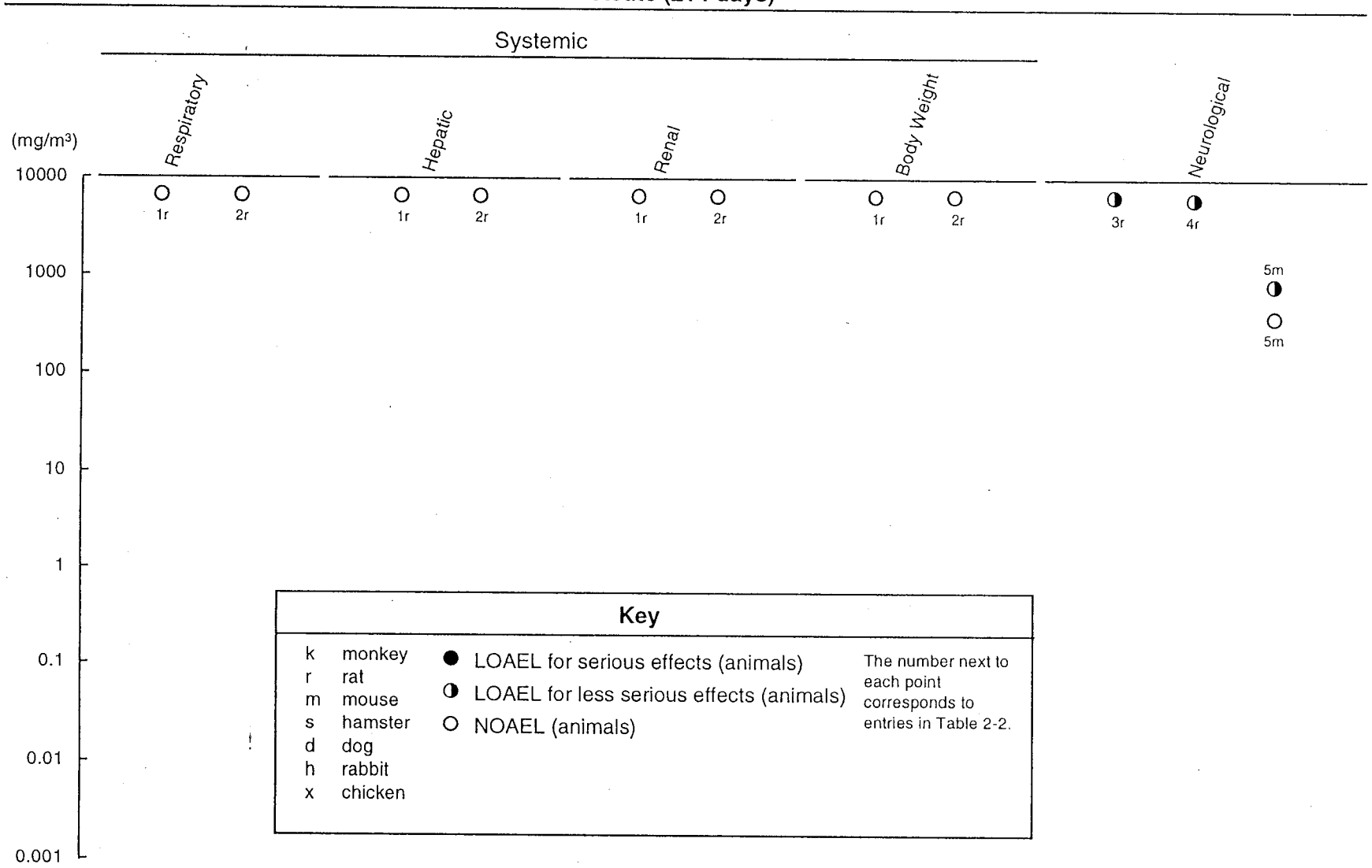


Figure 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids Inhalation (cont.)

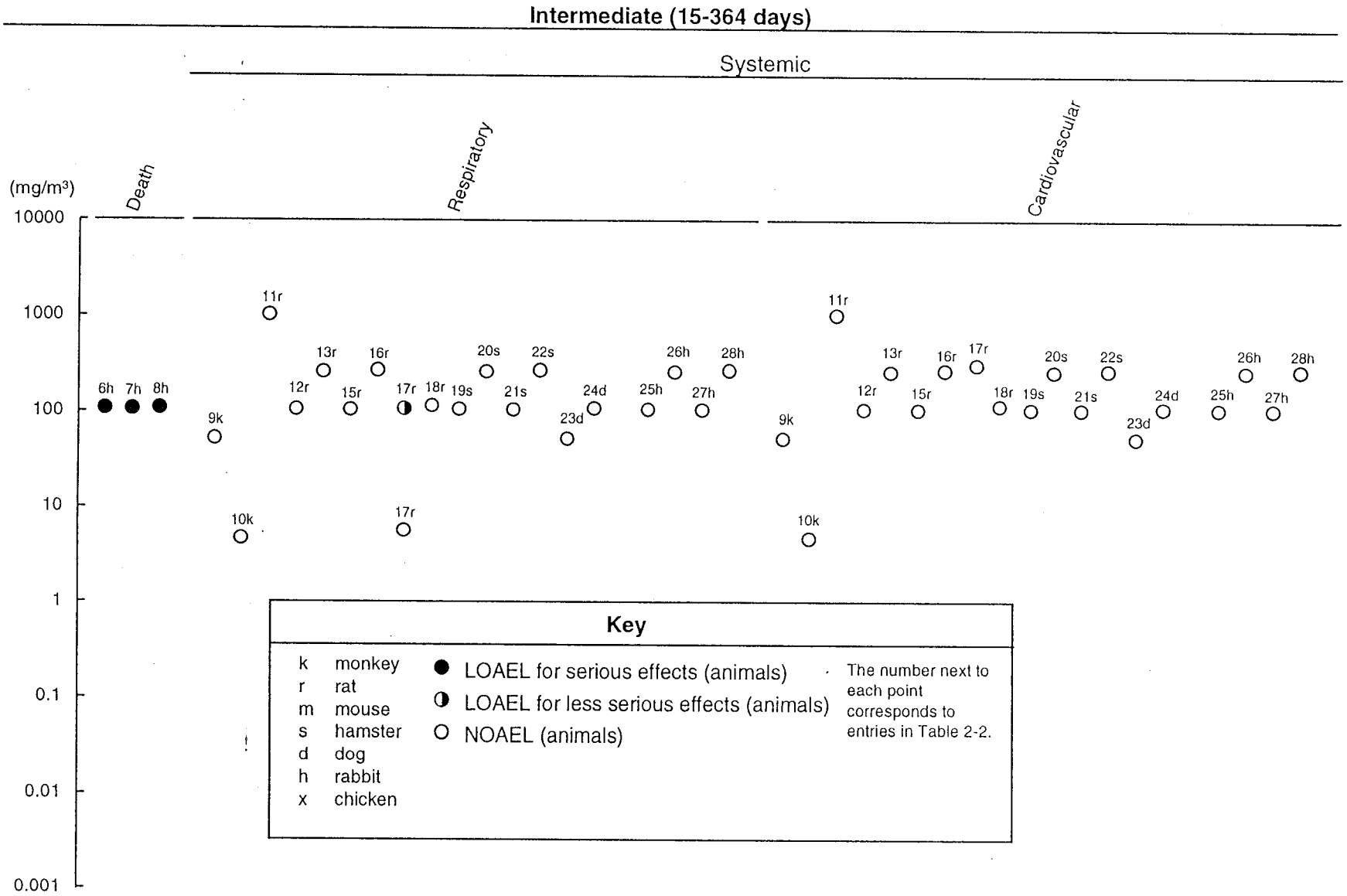


Figure 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids Inhalation (cont.)

Intermediate (15-364 days)

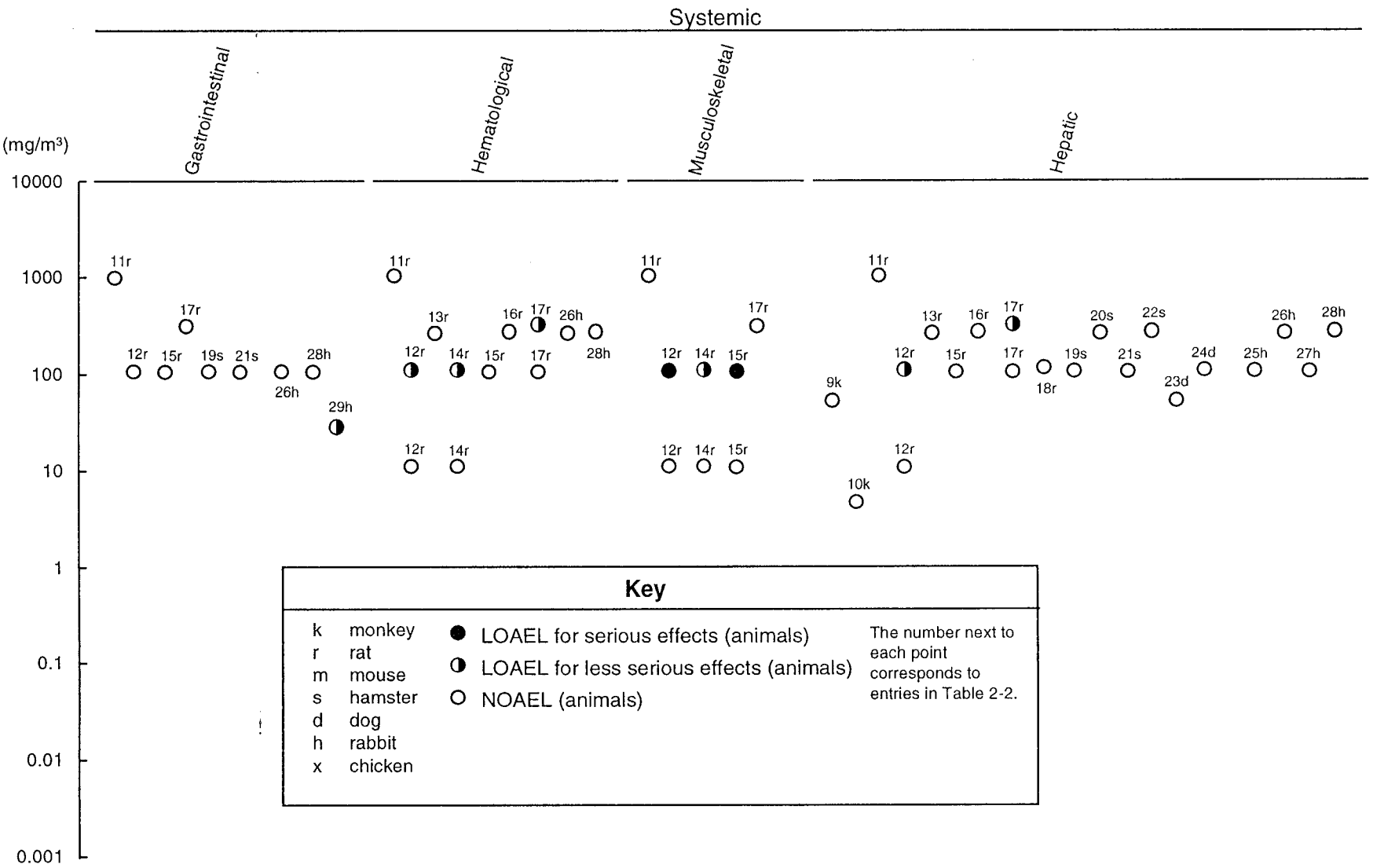


Figure 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids Inhalation (cont.)

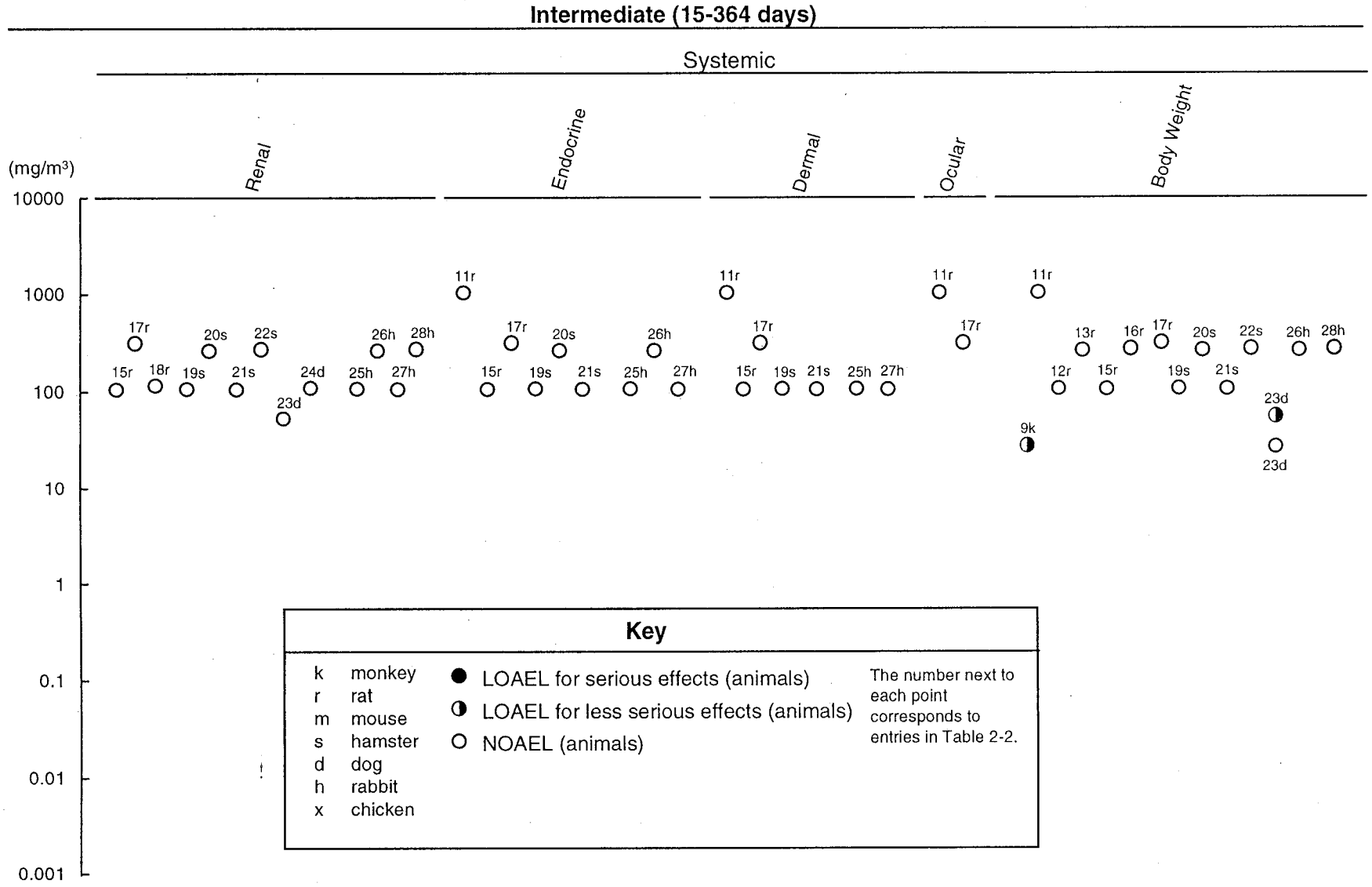


Figure 2-2. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids Inhalation (cont.)

Intermediate (15-364 days)

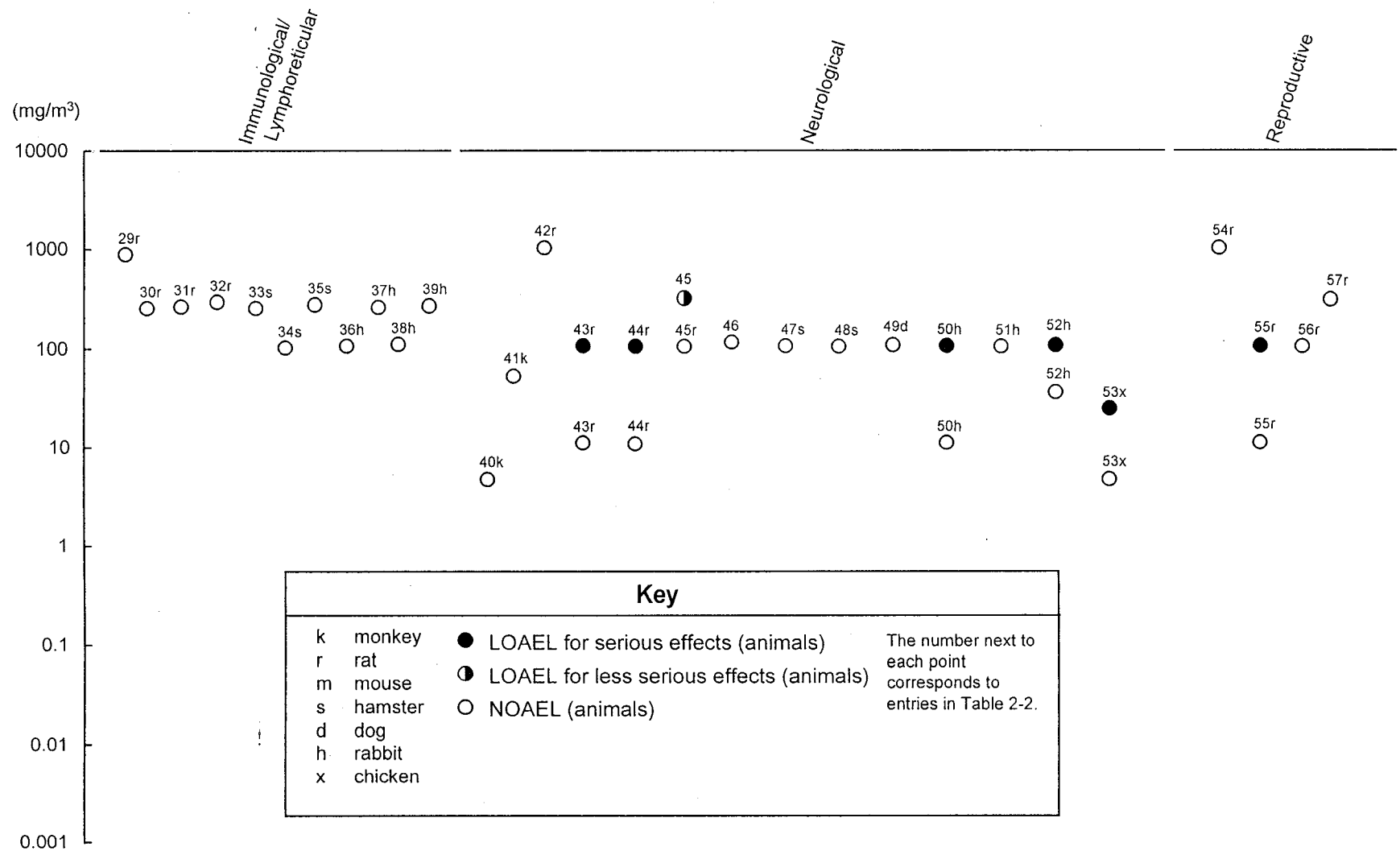


Table 2-3. Levels of Significant Exposure to Polyalphaolefin Hydraulic Fluids - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Fluid Identity
ACUTE EXPOSURE							
Death							
1	Rat (Sprague-Dawley)	4 hr				1620 M (LC_{50}) 1390 F (LC_{50})	Kinkead et al. 1987b (B85-174)
2	Rat (Sprague-Dawley)	4 hr				6430 (9/10 died)	MacEwen and Vernot 1983 (DTNSRDC N501)
3	Rat (Sprague-Dawley)	4 hr				2390 M (LC_{50}) 1670 F (LC_{50})	MacEwen and Vernot 1983 (DTNSRDC N501)
4	Rat (Fischer- 344)	4 hr				2130 M (LC_{50}) 1500 F (LC_{50})	Kinkead et al. 1992b (MIL-H-83282LT)
Systemic							
5	Rat (Sprague-Dawley)	4 hr	Resp			880 (congested lungs, bloody nasal discharge, rapid and shallow breathing)	Kinkead et al. 1987b (B85-174)
			Musc/skel			880 (kyphosis)	
6	Rat (Sprague-Dawley)	4 hr	Bd Wt	5430			MacEwen and Vernot 1983 (DTNSRDC N517)
7	Rat (Sprague-Dawley)	4 hr	Bd Wt	5350			MacEwen and Vernot 1983 (DTNSRDC N518)

Table 2-3 Levels of Significant Exposure to Polyalphaolefin Hydraulic Fluids - Inhalation (continued)

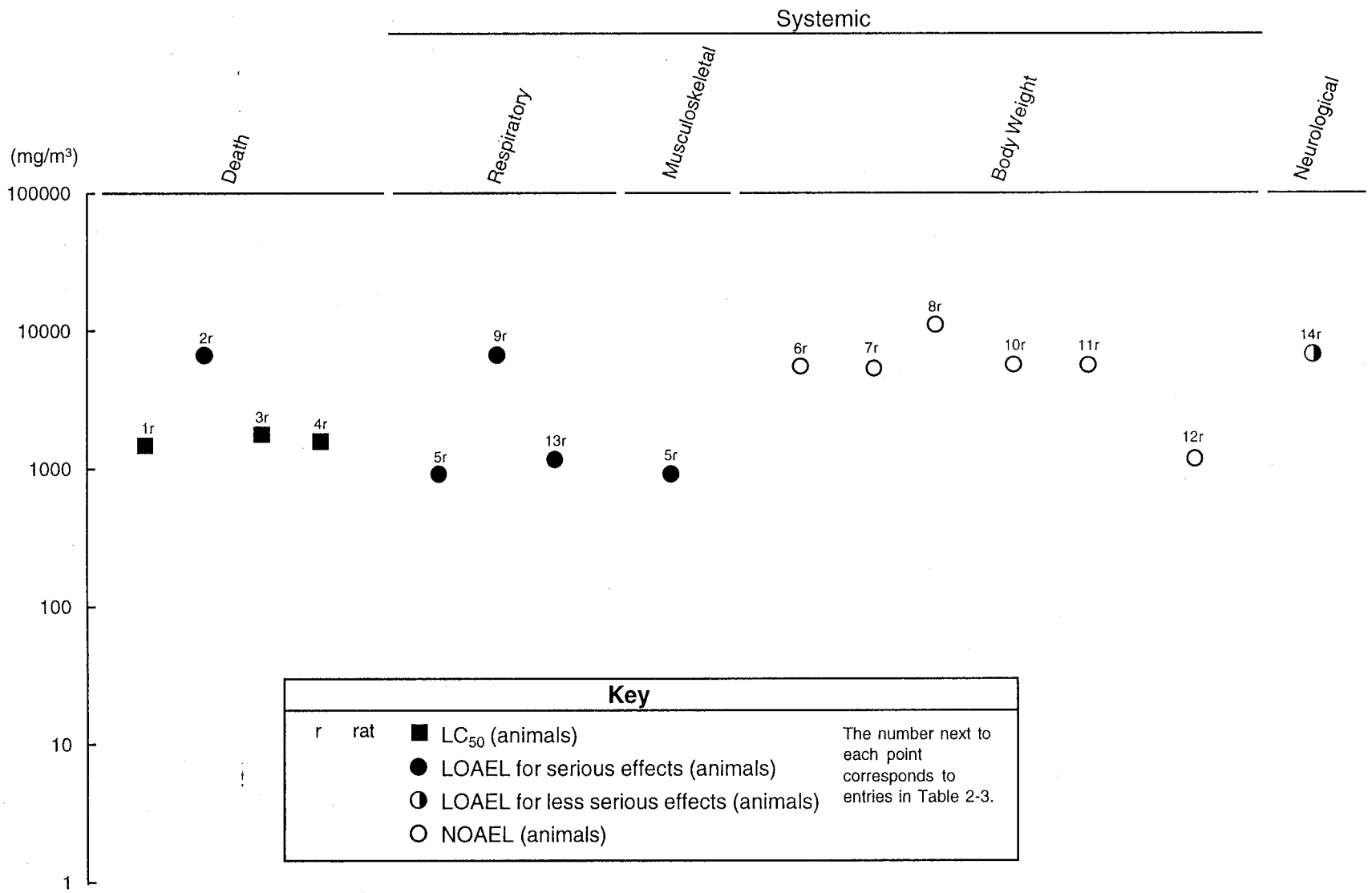
Key to figure[a]	Species/ (strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)		Reference Fluid Identity
8	Rat (Sprague-Dawley)	4 hr	Bd Wt	10720				MacEwen and Vernot 1983 (DTNSRDC N448)
9	Rat (Sprague-Dawley)	4 hr	Resp			6430	(labored breathing)	MacEwen and Vernot 1983 (DTNSRDC N501)
10	Rat (Sprague-Dawley)	4 hr	Bd Wt	5330				MacEwen and Vernot 1983 (DTNSRDC N525)
11	Rat (Sprague-Dawley)	4 hr	Bd Wt	5470				MacEwen and Vernot 1983 (DTNSRDC N527)
12	Rat (Sprague-Dawley)	6 hr	Bd Wt	1130				Kinkead et al. 1985 (MIL-H-83282)
13	Rat (Fischer- 344)	4 hr	Resp			1120	(severe acute irritation of the respiratory system, perivascular and peribronchial edema)	Kinkead et al. 1992b (MIL-H-83282LT)
	Neurological							
14	Rat (Sprague-Dawley)	4 hr			6430	(lethargy)		MacEwen and Vernot 1983 (DTNSRDC .N501)

[a]The number corresponds to entries in Figure 2-3.

Bd Wt = body weight; F = female; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect-level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory

Figure 2-3. Levels of Significant Exposure to Polyalphaolefin Hydraulic Fluids - Inhalation

Acute (≤14 days)



2. HEALTH EFFECTS

Houghto-Safe 5047F (Kinkead et al. 1991). A U.S. military fluid designated as MLH-5606 likewise produced no deaths in rats within 14 days of single 6-hour exposures to an aerosol concentration of 1,148 mg/m^3 (Kinkead et al. 1985). Additional information on lethality of mineral oil hydraulic fluids in animals after inhalation exposure was not located. The available mineral oil hydraulic fluid studies (presented in Table 2-l and Figure 2-l) were not designed to examine lethality, and probably did not use high enough concentrations to cause death.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding death in humans after inhalation exposure to organophosphate ester hydraulic fluids.

Single 4-hour exposures to aerosols of U.S. military fluids Durad MP280 and Fyrquel 220 produced no deaths in male rats at respective concentrations of 6,190 and 5,790 mg/m^{3}and female rats exposed to 6,350 and 6,310 mg/m^3, respectively (Gaworski et al. 1986; Kinkead et al. 1992a). Daily 4-hour exposures over an 1 l-day period caused death to a single rabbit exposed to 2,000 mg/m^3 of Cellulube 220 (Carpenter et al. 1959).

Intermediate-duration inhalation exposures to aerosols of a few organophosphate ester hydraulic fluids (Durad MP280 and trial phosphate ester") produced lethal neurotoxic effects in chickens and rabbits (MacEwen and Vemot 1983; Siegel 1965). Rats and hamsters appear to be less susceptible to the neurotoxic action of organophosphate esters; tests of several organophosphate fluids produced no deaths in rats exposed to substantial aerosol concentrations.

Aerosols of Cellulube 220 produced deaths associated with severe dyspnea and mild diarrhea in one of two rabbits exposed to 2,000 mg/m^3 for ≤4 hours/day, 5 days/week for 11 or 22 days (Carpenter et al. 1959). Continuous exposure for ~30-160 days to aerosols of a triaryl phosphate U.S. military hydraulic fluid (see Table 3-2), at concentrations ≤110 mg/m^3, produced no deaths in dogs or rats, but deaths associated with severe neurotoxic symptoms occurred in chickens exposed to concentrations ≥23 mg/m^3 and in rabbits exposed to 102 mg/m^3 (Siegel et al. 1965). Aerosols of Durad MP280 or Fyrquel 220 (continuous exposure for 90 days) produced no deaths in rats or hamsters exposed to 100 mg/m^3. Deaths associated with lethargy, cachexia, and head droop occurred in rabbits exposed to 101 mg/m^3 Durad MP280, but not in rabbits exposed to 100 mg/m^3 Fyrquel 220 (MacEwen and Vemot 1983). Some of the Durad MP280-exposed rabbits were also infected with *Pasteurella,* which may have contributed to neurological symptoms. No deaths occurred in rats exposed to cyclotriphosphazene at 990 mg/m^3, 6 hours/day, 5 days/week for 21 days

(Kinkead et al. 1989a, 1990) or in rats exposed to aerosols of Skydrol 500B-4 at concentrations ≤300 mg/m^3, 6 hours/day, 5 days/week for 13 weeks (Healy et al. 1992; Monsanto 1987a, 1987b, 1989). The LOAEL values for death are presented in Table 2-2 and Figure 2-2.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding death in humans after inhalation exposure to polyalphaolefin hydraulic fluids.

The LC_{50} values (single 4-hour exposures) for male and female rats, respectively, were determined for several U.S. military polyalphaolefin hydraulic fluids as follows: DTNSRDC N501, 2, 390 and 1,670 mg/m^3 (MacEwen and Vemot 1983); MIL-H-83282LT, 2,130 and 1,500 mg/m^3 (Kinkead et al. 1992b); and B85-174, 1,620 and 1,390 mg/m^3 (Kinkead et al. 1987b). Kinkead et al. (1992b) speculated from observations of pulmonary edema in the dead rats that deaths were caused by acute respiratory irritation. Several other U.S. military fluids produced no deaths in rats within 14 days of single 4-hour exposures to the following aerosol concentrations: DTNSRDC N527, 5, 470 mg/m^3; DTNSRDC N448, 10, 720 mg/m^3; DTNSRDC N518,5,350 mg/m^3; DTNSRDC N517, 5, 430 mg/m^3; and DTNSRDC N525, 5, 470 mg/m^3 (MacEwen and Vemot 1983). These acute-duration LOAEL values for death are recorded in Table 2-3 and Figure 2-3.

2.2.1.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Tables 2-1,2-2, and 2-3 and plotted in Figures 2-1,2-2, and 2-3 for mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, and polyalphaolefin hydraulic fluids, respectively. Data for systemic effects (respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, and ocular) from chicken studies were not presented in the LSE tables or figures because the appropriateness of nonmammalian models for human systemic effects is not known. However, chickens have been shown to be a sensitive species for neurological effects, and data from chickens are included in both the LSE tables and figures.

Respiratory Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding respiratory effects in humans after inhalation exposure to mineral oil hydraulic fluids.

2. HEALTH EFFECTS

Histopathological examination of the lungs from male and female Fischer 344 rats exposed to ≤1.0 mg/m^3 of the water-in-oil emulsion hydraulic fluid Houghto-Safe 5047F for 90 days, 23 hours/day, showed no treatment-related lesions (Kinkead et al. 1991).

Organophosphate Ester Hydraulic Fluids. No studies were located regarding respiratory effects in humans after inhalation exposure to organophosphate ester hydraulic fluids.

Single 4-hour exposures to aerosols of U.S. military fluids Durad MP280 and Fyrquel220 produced no adverse respiratory effects in male Sprague-Dawley rats at respective concentrations of 6,190 and 5,790 mg/m^3 and female Sprague-Dawley rats exposed to 6,350 and 6,310 mg/m^3, respectively (Gaworski et al. 1986; Kinkead et al. 1992a). Acute exposure to ≈6,300 mg/m^3 of Fyrquel 220 (Gaworski et al. 1986; Kinkead et al. 1992a) or Durad MP280 (Gaworski et al. 1986) did not result in respiratory tract damage in rats.

Following intermediate-duration exposure to organophosphate ester hydraulic fluids, reversible rapid respirations were observed in rabbits exposed to 2,000 mg/m^3 of a triaryl phosphate hydraulic fluid (Cellulube 220) (Carpenter et al. 1959) and reddish nasal discharge (likely to be indicative of respiratory tract irritation) was observed in rats exposed to 100 mg/m^3 of Skydrol 500B-4 (Healy et al. 1992; Monsanto 1987a, 1987b, 1989). The NOAEL for nasal discharge was 5.3 mg/m^3. Most studies that examined the respiratory tract did not find gross or histological alterations. Intermediate-duration exposure of rats, rabbits, dogs, hamsters, or monkeys to Fyrquel 220 (Gaworski et al. 1986; MacEwen and Vemot 1983), Durad MP280 (Gaworski et al. 1986; MacEwen and Vemot 1983), and triaryl phosphate (Siegel et al. 1965) also did not result in adverse respiratory tract effects. The NOAEL values following intermediate-duration exposure ranged from 100 to 260 mg/m^3 for rats, 50 to 260 mg/m^3 for rabbits, 50 to 103 mg/m^3 for dogs, 100 to 260 mg/m^3 for hamsters, and 4.4 to 50 mg/m^3 for monkeys. It should be noted that the 90-day NOAELs for Durad MP280 and Fyrquel 220 in rats, hamsters, and rabbits were based on gross pathology only (MacEwen and Vemot 1983). Intermediate-duration exposure to 990 mg/m^3 cyclotriphosphazene had no adverse respiratory effects on rats (Kinkead et al. 1989a, 1990). No chronic-duration inhalation studies examining the respiratory tract were located.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding respiratory effects in humans after inhalation exposure to polyalphaolefin hydraulic fluids.

2. HEALTH EFFECTS

Certain polyalphaolefin hydraulic fluids appear to be respiratory tract irritants in animals. Bloody nasal discharge, rapid and shallow breathing, and lung congestion have been observed in rats exposed to 880 mg/m^3 of a polyalphaolefin hydraulic fluid designated as B85-174 for 4 hours (Kinkead et al. 1987b). Exposure to a lethal concentration (1,120 mg/m^3) of a polyalphaolefin designated as MIL-H-83282LT resulted in perivascular and peribronchial edema in rats (Kinkead et al. 1992b). Labored breathing has also been observed in rats exposed for 4 hours to a lethal concentration (6,430 mg/m^3) of a polyalphaolefin hydraulic fluid designated as DTNSRDC N501 (MacEwen and Vet-not 1983). No longer-term studies examining respiratory effects were located.

Cardiovascular Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding cardiovascular effects in humans after inhalation exposure to mineral oil hydraulic fluids.

Histopathological examination of the heart from male and female Fischer 344 rats exposed to ≤1 .0 mg/m^3 of the water-in-oil emulsion hydraulic fluid Houghto-Safe 5047F for 90 days, 23 hours/day, showed no treatment-related lesions (Kinkead et al. 1991).

Organophosphate Ester Hydraulic Fluids. No studies were located regarding cardiovascular effects in humans after inhalation exposure to organophosphate ester hydraulic fluids.

Following intermediate-duration exposure, no cardiovascular effects were observed in rats, rabbits, hamsters, dogs, or monkeys exposed to Durad MP280 (Gaworski et al. 1986; MacEwen and Vemot 1983), Fyrquel220 (Gaworski et al. 1986; MacEwen and Vemot 1983), Skydrol 500B-4 (Healy et al. 1992; Monsanto 1987a, 1987b, 1989), cyclotriphosphazene (Kinkead et al. 1989a, 1990), Cellulube 220 (Carpenter et al. 1959) or triaryl phosphate hydraulic fluids (Siegel et al. 1965). The ranges of NOAEL values were 100-260 mg/m^3 for rats, 251-2,000 mg/m^3 for rabbits, 100-260 mg/m^3 for hamsters, 50-103 mg/m^3 for dogs, and 4.4-50 mg/m^3 for monkeys. It should be noted that the 90-day NOAELs for Durad MP280 arid Fyrquel 220 in rats, hamsters, and rabbits were based on gross pathology only (MacEwen and Vemot 1983). Intermediate-duration exposure to 990 mg/m^3 cyclotriphosphazene had no adverse cardiovascular effects on rats (Kinkead et al. 1989a, 1990). No studies examining cardiovascular end points following acute-or chronic-duration inhalation exposure were located.

2. HEALTH EFFECTS

Polyalphaolefm Hydraulic Fluids. No studies were located regarding cardiovascular effects in humans or animals after inhalation exposure to polyalphaolefin hydraulic fluids.

Gastrointestinal Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding gastrointestinal effects in humans or animals after inhalation exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to organophosphate ester hydraulic fluids.

Mild diarrhea was reported for an acute-duration study on a single rabbit exposed to Cellulube 220 (Carpenter et al. 1959), and transient diarrhea was reported in rabbits exposed to 26 mg/m^3 Fyrquel 220 for 21 days for 6 hours a day (Gaworski et al. 1986; MacEwen and Vernot 1983). In most studies, diarrhea and/or gross or histological alterations in the gastrointestinal tract have not been observed in rats, rabbits, or hamsters exposed to organophosphate ester hydraulic fluids for an intermediate duration. NOAEL values of 100-260 mg/m^3, l00-2,000 mg/m^3, and 100-101 mg/m^3 in rats, rabbits, and hamsters, respectively, exposed to Durad MP280 (Gaworski et al. 1986; MacEwen and Vemot 1983), Fyrquel220 (Gaworski et al. 1986; MacEwen and Vemot 1983), and Skydrol 500B-4 (Healy et al. 1992; Monsanto 1987a, 1987b, 1989). It should be noted that the 90-day NOAELs for Durad MP280 and Fyrquel 220 in rats, hamsters, and rabbits were based on gross pathology only (MacEwen and Vemot 1983). Cellulube 220 exposure in rabbits was associated with salivation, although this may have been a neurological response (Carpenter et al. 1959). Intermediate-duration exposure to 990 mg/m^3 cyclotriphosphazene had no adverse gastrointestinal effects on rats (Kinkead et al. 1989a, 1990). No chronic-duration inhalation studies examining gastrointestinal end points were located.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding gastrointestinal effects in humans or animals after inhalation exposure to polyalphaolefin hydraulic fluids.

Hematological Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding hematological effects in humans or animals after inhalation exposure to mineral oil hydraulic fluids.

2. HEALTH EFFECTS

Organophosphate Ester Hydraulic Fluids. In a study of nonspecific monocyte esterase staining, humans who were exposed to aryl phosphates occupationally showed very slight esterase inhibition (Mandel et al. 1959).

Two studies reported hematological effects in animals exposed to organophosphate ester hydraulic fluids for an intermediate duration. Significant decreases in erythrocyte, hemoglobin, and hematocrit levels were observed in rats exposed to 300 mg/m^3 of Skydrol 500B-4 (Healy et al. 1992; Monsanto 1987a, 1987b, 1989), and leukocytosis was observed in male rats exposed to 101 mg/m^3 Durad MP280 (MacEwen and Vemot 1983). The NOAEL values for these studies were 100 mg/m^3 for Skydrol 500B-4 and 10.3 mg/m^3 for Durad MP280.

A number of other animal studies have monitored hematological parameters, but have not found biologically significant alterations. The identified highest NOAEL values following intermediate exposure identified in other studies are 251 mg/m^3 for rats and rabbits exposed to Durad MP280 (Gaworski et al. 1986; MacEwen and Vemot 1983), 260 mg/m^3 for rats and rabbits exposed to Fyrquel 220 (Gaworski et al. 1986; MacEwen and Vemot 1983), and 990 mg/m^3 for rats exposed to cyclotriphosphazene (Kinkead et al. 1989a, 1990).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding hematological effects in humans or animals after inhalation exposure to polyalphaolefin hydraulic fluids.

Musculoskeletal Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to organophosphate ester hydraulic fluids.

In animals, the only musculoskeletal effect observed was kyphosis, a deformity of the spine characterized by extensive flexion. Kyphosis was observed in rats exposed to 100 mg/m^3 of Fyrquel 220 and 101 mg/m^3 of Durad MP280 for an intermediate duration (MacEwen and Vemot 1983). The kyphosis was not observed at ≈10 mg/m^3. It is not known whether the kyphosis was due to neurological or musculoskeletal damage. See Section 2.2.1.4 for more information on the neurological effects of organophosphate ester hydraulic fluids.

2. HEALTH EFFECTS

Following intermediate-duration exposure, no histological damage was observed in the skeletal muscle of rats exposed to 990 mg/m^3 of cyclotriphosphazene (Kinkead et al. 1989a, 1990) or rabbits exposed to 2,000 mg/m^3 of Cellulube 220 (Carpenter et al. 1959). Similar results were found in rats exposed to ≤300 mg/m^3 of Skydrol 500B-4 (Healy et al. 1992; Monsanto 1987a, 1987b, 1989).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to polyalphaolefin hydraulic fluids.

Kyphosis, a deformity of the spine characterized by extensive flexion, was observed in rats exposed to 880-5030 mg/m^3 of a polyalphaolefin hydraulic fluid designated as B85-174 for 4 hours (Kinkead et al. 1987b). The authors did not specify at which concentration the kyphosis occurred. It is not known whether the kyphosis was due to neurological or musculoskeletal damage. See Section 2.2.1.4 for more information on the neurological effects of polyalphaolefin hydraulic fluids. No longer-term inhalation exposure studies were located.

Hepatic Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding hepatic effects in humans after inhalation exposure to mineral oil hydraulic fluids.

Histopathological examination of the liver from male and female Fischer 344 rats exposed to ≤1.0 mg/m^3 of the water-in-oil emulsion hydraulic fluid Houghto-Safe 5047F for 90 days, 23 hours/day, showed no treatment-related lesions (Kinkead et al. 1991).

Organophosphate Ester Hydraulic Fluids. No studies were located regarding hepatic effects in humans after inhalation exposure to organophosphate ester hydraulic fluids.

Following acute exposure, a NOAEL of 6,350 mg/m^3 has been identified in rats exposed to Durad MP280 (Gaworski et al. 1986), and 6,310 mg/m^3 in rats exposed to Fyrquel 220 (Gaworski et al. 1986; Kinkead et al. 1992a). Significant increases in absolute and/or relative liver weights have been observed in rats exposed to 100 or 260 mg/m^3 of Fyrquel220 (Gaworski et al. 1986; MacEwen and Vernot 1983) and 101 or 25 1 mg/m^3 of Durad MP280 (Gaworski et al. 1986; MacEwen and Vernot 1983) for intermediate durations. However, histological alterations have not been observed in rats, rabbits, hamsters, dogs, monkeys, or

chickens exposed to Durad MP280 (Gaworski et al. 1986; MacEwen and Vemot 1983), Fyrquel 220 (Gaworski et al. 1986; Kinkead et al. 1992a; MacEwen and Vemot 1983), Skydrol 500B-4 (Healy et al. 1992; Monsanto 1987a, 1987b, 1989) Cellulube 220 (Carpenter et al. 1959) and triaryl phosphate (Siegel et al. 1965). Thus, the changes in liver weight were not considered adverse. Mild hepatocellular vacuolation and significant increases in absolute and relative liver weights were observed in rats exposed to 300 mg/m^3 Skydrol 500B-4 for 13 weeks; no hepatic effects were observed in the 100 mg/m^3 group (Healy et al. 1992; Monsanto 1987a, 1987b, 1989). The authors noted that since there were no other histological alterations in the liver or changes in hepatic serum enzymes at any concentration, these effects were not considered adverse. No hepatic effects were observed in other intermediate-duration inhalation studies. The NOAEL values for liver effects following intermediate-duration exposure to organophosphate ester hydraulic fluids are 100-260 mg/m^3 for rats, 251-2,000 mg/m^3 for rabbits, 100-260 mg/m^3 for hamsters, 50-103 mg/m^3 for dogs, and 4.4-50 mg/m^3 for monkeys. It should be noted that the 90-day NOAELs for Durad MP280 and Fyrquel220 in rats, hamsters, and rabbits were based on gross pathology only (MacEwen and Vemot 1983). Intermediate-duration exposure to 990 mg/m^3 cyclotriphosphazene had no adverse hepatic effects on rats (Kinkead et al. 1989a, 1990). No chronic exposure studies examining hepatic end points were located.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding hepatic effects in humans or animals after inhalation exposure to polyalphaolefin hydraulic fluids.

Renal Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding renal effects in humans after inhalation exposure to mineral oil hydraulic fluids.

Histopathological examination of the kidneys from male and female Fischer 344 rats exposed to ≤1.0 mg/m^3 of the water-in-oil emulsion hydraulic fluid Houghto-Safe 5047F for 90 days, 23 hours/day, showed no treatment-related lesions (Kinkead et al. 1991).

Organophosphate Ester Hydraulic Fluids. No studies were located regarding renal effects in humans after inhalation exposure to organophosphate ester hydraulic fluids.

2. HEALTH EFFECTS

No gross or histological alterations were observed in the kidneys of rats exposed to 6,350 mg/m^3 of Durad MP280 (Gaworski et al. 1986) or to 6,310 mg/m^3 of Fyrquel 220 (Gaworski et al. 1986; Kinkead et al. 1992a) for single 4-hour periods. Significant increases in absolute and relative kidney weights were observed in rats exposed to 100 mg/m^3 of Fyrquel 220 for an intermediate duration (MacEwen and Vemot 1983). However, no gross or histological lesions were observed at this or a higher concentration (260 mg/m^3) for a shorter duration (Gaworski et al. 1986; MacEwen and Vemot 1983). Thus, this change in kidney weight was not considered adverse. A number of intermediate-duration studies have identified NOAEL values in rats, rabbits, hamsters, dogs, monkeys, and chickens exposed to Durad MP280 (Gaworski et al. 1986; MacEwen and Vemot 1983), Fyrquel 220 (Gaworski et al. 1986; MacEwen and Vemot 1983), Skydrol 500B-4 (Healy et al. 1992; Monsanto 1987a, 1987b, 1989), Cellulube 220 (Carpenter et al. 1959), and triaryl phosphate (Siegel et al. 1965). The NOAEL values for renal effects following intermediate-duration exposure to organophosphate ester hydraulic fluids are 100-260 mg/m^3 for rats, 251-2,000 mg/m^3 for rabbits, 100-260 mg/m^3 for hamsters, 50-103 mg/m^3 for dogs, and 4.4-50 mg/m^3 for monkeys. It should be noted that the 90-day NOAELs for Durad MP280 and Fyrquel 220 in rats, hamsters, and rabbits were based on gross pathology only (MacEwen and Vemot 1983). An accumulation of hyaline droplets was observed in male and female rats exposed to ≥240 mg/m^3 of cyclotriphosphazene for an intermediate duration (Kinkead et al. 1989a, 1990). The severity of the droplet accumulation was graded as minimal to mild. No changes in serum creatinine or urea nitrogen levels were observed in this study. No chronic exposure studies examining renal end points were located.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding renal effects in humans or animals after inhalation exposure to polyalphaolefin hydraulic fluids.

Endocrine Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding endocrine effects in humans or animals after inhalation exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding endocrine effects in humans after inhalation exposure to organophosphate ester hydraulic fluids.

No endocrine effects were seen in acute inhalation exposure to a triaryl phosphate mixture (Cellulube 220) for rabbits at 2,000 mg/m^3 (Carpenter et al. 1959). In studies on rats, hamsters and rabbits no endocrine

effects are reported for intermediate-duration exposure to 300 mg/m^3 Skydrol 500B-4 (Healy et al. 1992; Monsanto 1987a, 1987b, 1989), 100 mg/m^3 Fyrquel 220 or 101 mg/m^3 Durad MP280 (MacEwen and Vemot 1983), or 2,000 mg/m^3 of Cellulube 220 (Carpenter et al. 1959). It should be noted that the 90-day NOAELs for Durad MP280 and Fyrquel 220 in rats, hamsters, and rabbits were based on gross pathology only (MacEwen and Vemot 1983).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding endocrine effects in humans or animals after inhalation exposure to polyalphaolefin hydraulic fluids.

Dermal Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding dermal effects in humans or animals after inhalation exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding dermal effects in humans after inhalation exposure to organophosphate ester hydraulic fluids.

No gross or histological alterations were observed in the skin of rats, rabbits, or hamsters exposed to 100 mg/m^3 of Fyrquel 220 or 101 mg/m^3 of Durad MP280 (MacEwen and Vemot 1983), or G ≤300 mg/m^3 Skydrol 500B-4 (Healy et al. 1992; Monsanto 1987a, 1987b, 1989), or ≤990 mg/m^3 cyclotriphosphazene (Kinkead et al. 1989a, 1990) for an intermediate duration, or in rabbits exposed to 2,000 mg/m^3 of Cellulube 220 for acute and intermediate durations (Carpenter et al. 1959). It should be noted that the 90-day NOAELs for Durad MP280 and Fyrquel 220 in rats, hamsters, and rabbits were based on gross pathology only (MacEwen and Vemot 1983).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding dermal effects in humans after inhalation exposure to polyalphaolefin hydraulic fluids.

Ocular Effects.

Mineral Oil Hydraulic FLuids. No studies were located regarding ocular effects in humans or animals after inhalation exposure to mineral oil hydraulic fluids.

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Organophosphate Ester Hydraulic Fluids. No studies were located regarding ocular effects in humans after inhalation exposure to organophosphate ester hydraulic fluids.

No histological evidence of damage to the eye was observed in rats exposed to 990 mg/m^3 of cyclotriphosphazene for an intermediate duration (Kinkead et al. 1989a, 1990).

Polyalphaolefm Hydraulic Fluids. No studies were located regarding ocular effects in humans after inhalation exposure to polyalphaolefin hydraulic fluids. Ocular effects in animals resulting from direct contact with aerosols of polyalphaolefin hydraulic fluids are discussed in Section 2.3, Dermal Effects.

Body Weight Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding body weight effects in humans after inhalation exposure to mineral oil hydraulic fluids. In rats, no alterations in body weight gain were observed following 4-hour exposures to 180 mg/m^3 of Sunsafe F (Kinkead et al. 1987a, 1988), 180 mg/m^3 of Quintolubric 95830W (Kinkead et al. 1987a, 1988), 210 mg/m^3 of Houghto-Safe 5047F (Kinkead et al. 1987a, 1988), or 110 mg/m^3 of Pyroguard A-443 (Kinkead et al. 1987a, 1988), or following a 6-hour exposure to 1,130 mg/m^3 of a mineral oil hydraulic fluid meeting military specifications of MJL-5606 (Kinkead et al. 1985). Body weight was unaffected in male and female Fischer 344 rats exposed to ≤1.0 mg/m^3 of the water-in-oil emulsion hydraulic fluid Houghto- Safe 5047F for 90 days, 23 hours/day (Kinkead et al. 1991).

Organophosphate Ester Hydraulic Fluids. No studies were located regarding body weight effects in humans after inhalation exposure to organophosphate ester hydraulic fluids.

No changes in body weight gain were observed in rats exposed for 4 hours to 6,350 mg/m^3 Durad MP280 (Gaworski et al. 1986; Kinkead et al. 1992d), or for 4 hours to 6,3 10 mg/m^3 Fyrquel 220 (Gaworski et al. 1986; Kinkead et al. 1992a). In intermediate-duration studies, an 11% loss of body weight occurred in squirrel monkeys exposed to 25 mg/m^3 of a triaryl phosphate mixture for 6 weeks (Siegel et al. 1965). In other studies, no adverse changes in body weight or weight gain were reported in monkeys, rats, rabbits, hamsters, and dogs exposed for intermediate durations to Fyrquel 220 (Gaworski et al. 1986; MacEwen and Vemot 1983), Durad MP280 (Gaworski et al. 1986; MacEwen and Vemot 1983), Skydrol 500B-4 (Healy et

al. 1992; Monsanto 1987a, 1987b, 1989), or triaryl phosphate (Siegel et al. 1965). The identified NOAEL values ranged from 100 to 260 mg/m^3 for rats, 25 1 to 260 for rabbits, 100 to 260 mg/m^3 for hamsters, and 50 to 103 mg/m^3 for dogs, and 4.4 mg/m^3 for monkeys. Intermediate-duration exposure to 990 mg/m^3 cyclotriphosphazene had no effect on body weight in rats (Kinkead et al. 1989a, 1990). No chronic-duration exposure studies examining body weight end points were located.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding body weight effects in humans after inhalation exposure to polyalphaolefin hydraulic fluids.

No changes in body weight gain were observed in rats exposed for 4 hours to several polyalphaolefin hydraulic fluids at the following concentrations: 10,720 mg/m^3 - DTNSRDC N448; 5,430 mg/m^3 - DTNSRDC N517; 5,350 mg/m^3 - DTNSRDC N518; 5,330 mg/m^3 - DTNSRDC N525; 5,470 mg/m^3 - DTNSRDC N527 (all fluids with a DTNSRDC number were tested by MacEwen and Vernot [1983]); 1,130 mg/m^3 – MIL-H-83282 (Kinkead et al. 1985). In these experiments, rats were observed for 14 days after exposure.

2.2.1.3 Immunological and Lymphoreticular Effects

Mineral Oil Hydraulic Fluids. No studies were located regarding immunological effects in humans or animals after inhalation exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding immunological effects in humans after inhalation exposure to organophosphate ester hydraulic fluids.

Information regarding immunological effects in animals is restricted to histopathological examination of organs with immune functions (thymus, spleen, lymph nodes) after intermediate-duration inhalation exposures of up to 90 days. No treatment-related lesions in these tissues was reported in rats exposed to ≤900 mg/m^3 cyclotriphosphazene (Kinkead et al. 1989b, 1990). No lesions were seen in the spleen of rats exposed to 260 mg/m^3 Fyrquel 220 or 25 1 mg/m^3 Durad MP280 (Gaworski et al. 1986; MacEwen and Vernot 1983), or 300 mg/m^3 Skydrol 500B-4 (Healy et al. 1992; Monsanto 1987a, 1987a, 1989). Similar results were reported for the spleen in both hamsters and rabbits exposed to ≤260 mg/m^3 Fyrquel220 or 251 mg/m^3 Durad MP280 for 21 days (Gaworski et al. 1986; MacEwen and Vemot 1983). It should be noted that the 90-day NOAELs for Durad MP280 and Fyrquel 220 in rats, hamsters, and rabbits were based

on gross pathology only (MacEwen and Vernot 1983). The NOAEL values for immunological effects are recorded in Table 2-2 and plotted in Figure 2-2.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding immunological effects in humans or animals after inhalation exposure to polyalphaolefin hydraulic fluids.

2.2.1.4 Neurological Effects

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Tables 2-1,2-2, and 2-3 and plotted in Figures 2-1, 2-2, and 2-3 for mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, and polyalphaolefin hydraulic fluids, respectively.

Mineral Oil Hydraulic Fluids. No studies were located regarding neurological effects in humans after inhalation exposure to mineral oil hydraulic fluids. There are reports of neurological effects in humans occupationally exposed to mineral oil hydraulic fluids; however dermal contact was expected to have been the primary route of exposure (see Section 2.2.3.4).

Information regarding neurological effects in animals after inhalation exposure to mineral oil hydraulic fluids is limited to two rat studies in which no symptoms of acute neurotoxicity or delayed neuropathy were seen in rats within 14 days of aerosol exposure. (These studies did not specifically look for neurological effects.) One study exposed Fischer 344 rats for 4 hours to water-in-oil emulsion hydraulic fluids at concentrations ranging from 110 to 210 mg/m^3 (Pyroguard A-443, Houghto-Safe 5047F, Quintolubric 9583OW, and Sunsafe F) (Kinkead et al. 1987a, 1988). The second study exposed rats to 1,148 mg/m^3 of MIL-H-5606 for 6 hours (Kinkead et al. 1985).

Organophosphate Ester Hydraulic Fluids. The principal adverse effect of exposure to organophosphate esters is neurotoxicity. Organophosphate esters have been synthesized that-are preferentially toxic to insects compared to mammals; these are widely used as insecticides (e.g., chlorpyrifos, diazinon). Acute toxicity to organophosphate esters is mediated by the inhibition of neural acetylcholinesterase. Neural acetylcholinesterase is present at cholinergic synapses throughout the central and peripheral nervous systems, and is responsible for hydrolyzing acetylcholine released from the pre-synaptic terminal. If this enzyme is inhibited, acetylcholine accumulates in the synapse, resulting in increased firing of the post-

synaptic neuron or increased neuroeffector activity. The consequences of increased cholinergic activity in the parasympathetic autonomic nervous system (muscarinic receptors) can include increased salivation, lacrimation, perspiration, miosis, nausea, vomiting, diarrhea, excessive bronchial secretions, bradycardia, frequent micturition, and incontinence. The effects of increased neuroeffector activity on skeletal muscles (nicotinic receptors) can include muscle fasciculations, cramps, muscle weakness, and depolarization-type paralysis. Effects on cholinergic synapses in the central nervous system (predominantly muscarinic) can result in drowsiness, fatigue, mental confusion, headache, convulsions, and coma (see Table 2-10). These classical symptoms of organophosphate ester neurotoxicity increase in severity and rapidity of onset in a dose-dependent manner (Ecobichon 1991).

Acetylcholinesterase is also present in erythrocytes where it is known as erythrocyte acetylcholinesterase. Both forms of acetylcholinesterase are produced by the same gene (Taylor et al. 1993). In *in vitro* assays, erythrocyte and neural acetylcholinesterase are inhibited to roughly the same extent by exposure to many organophosphate esters. Measurement of erythrocyte acetylcholinesterase is used as a surrogate of the inhibition of neural acetylcholinesterase. A cholinesterase capable of hydrolyzing acetylcholine is also produced by the liver and circulates in the blood. This enzyme, called plasma cholinesterase or butyrylcholinesterase, can also be inhibited by organophosphate esters and is often used as a marker for exposure. The endogenous substrate of this enzyme is unknown. This enzyme is often inhibited by organophosphate esters at lower levels of exposure than required to inhibit neural or erythrocyte acetylcholinesterase. Erythrocyte acetylcholinesterase activity is located in the erythrocyte membrane and can be differentiated from plasma cholinesterase by sedimenting the erythrocytes from whole blood. Measurement of "whole blood cholinesterase" reflects both plasma and erythrocyte activity.

Exposure to organophosphate esters can also cause a syndrome referred to as organophosphate-induced delayed neuropathy (OPIDN). This is a syndrome observed in humans and some animal models after exposure to certain organophosphate esters, for example tri-*ortho*-cresyl phosphate (Johnson 1981). The initial clinical signs are disturbances of gait, usually seen at least a week after exposure has begun. Severe cases can result in ataxia and paralysis. A characteristic "dying-back" type degeneration of motor fibers is seen upon histopathological examination. The biochemical mechanism of OPIDN is unknown at the present time. This syndrome does not appear to be closely correlated with neural acetylcholinesterase inhibition, but rather an enzyme activity referred to as "neurotoxic esterase" (NTE). The endogenous substrate of this enzyme activity is unknown. This syndrome can be reproduced in chickens, but not in rats or mice (Abou-Donia and Lapadula 1990).

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One study was located regarding neurological effects in humans after inhalation exposure to organophosphate ester hydraulic fluids. Workers in an aryl phosphate manufacturing plant were not found to have neurological deficits even with decades of potential exposure (Reade 1982).

Information regarding neurological effects in animals after acute inhalation exposure to organophosphate ester hydraulic fluids is limited to reports of a decrease in whole blood cholinesterase in mice exposed to 757 mg/m^3 of triphenyl phosphate (Sutton et al. 1960) and of head droop, generalized weakness, and decreased whole blood cholinesterase activity in one of two rabbits exposed to aerosols of 2,000 mg/m^3 Cellulube 220,4 hours/day, 5 days/week for 11 days (Carpenter et al. 1959). Transient, mild lethargy after 4-hour exposures to aerosols of Durad MP280 and Fyrquel 220 has been observed (Gaworski et al. 1986; Kinkead et al. 1992a).

Several organophosphate ester hydraulic fluids have produced neurological effects in several animal species after intermediate inhalation exposure (see Table 2-2).

Aerosols of Skydrol 500B-4 produced transient excessive salivation in rats exposed to 300 mg/m^3, 6 hours per day, 5 days per week for 6 or 13 weeks; this effect was not observed with exposure to 100 mg/m^3 by the same protocol (Healy et al. 1992; Monsanto 1987a, 1987b, 1989). Plasma cholinesterase activity (a marker for organophosphate ester exposure) was decreased 60% in this group; erythrocyte acetylcholinesterase was not measured in this study. Aerosols of Cellulube 220 produced decreased whole blood cholinesterase activity (13-57%) in rabbits exposed to 2,000 mg/m^3 for 4 hours/day, 5 days/week for 22 days; exposure for 2 hours/day produced no clinical signs of neurotoxicity in two rabbits (Carpenter et al. 1959). No overt signs of neurotoxicity or histological alterations of brain or sciatic nerve tissues were observed in rats exposed to cyclotriphosphazene at 990 mg/m^3, 6 hours/day, 5 days/week for 21 days (Kinkead et al. 1989a, 1990).

Continuous exposure for ≈30-160 days to aerosols of a triaryl phosphate U.S. military hydraulic fluid, triaryl phosphate (see Table 3-l), produced paralysis in rabbits and chickens after exposure to 102 mg/m^3 and 23 mg/m^3, respectively, but not after exposure to respective concentrations of 34 mg/m^3 or 4.4 mg/m^3 (Siegel et al. 1965). Continuous exposure to triaryl phosphate at 110, 103, or 4.4 mg/m^3, respectively, produced no signs of neurotoxicity in rats after 36 days, dogs after 99 days, or monkeys after 108 days (Siegel et al. 1965). Intermittent exposure (8 hours/day, 5 days/week for 30 exposures) to 50 mg/m^3 triaryl phosphate produced no neurotoxic signs in squirrel monkeys (Siegel et al. 1965). Aerosols of Durad MP280 (continuous exposure for 90 days) produced kyphosis (a deformity of the spine characterized by extensive

flexion) and a decrease in the tail tip curl reflex in rats and anorexia, lethargy, cachexia, and head droop in rabbits after exposure to 101 mg/m^3; exposure to 10.3 mg/m^3 produced no signs of neurotoxicity in these species (MacEwen and Vernot 1983). Hamsters similarly exposed to 101 mg/m^3 Durad MP280 showed no evidence of neurotoxicity in this study. Aerosols of Fyrquel 220 (continuous exposure for 90 days) likewise produced kyphosis in rats at 100 mg/m^3, but no clinical signs of neurotoxicity in rabbits or hamsters at 100 mg/m^3 (MacEwen and Vernot 1983). Because of the uncertainty that the kyphosis observed in rats is a neurological or muscular effect, this effect has been discussed in both sections.

The studies by Siegel et al. (1965) and MacEwen and Vemot (1983) also included intermittent exposure experiments (8 or 6 hours/day, respectively, for 5 days/week) for shorter durations (30 exposures or 21 days, respectively). Neither Fyrquel 220 (260 mg/m^3) nor Durad MP280 (251 mg/m^3) produced signs of neurotoxicity in rats, rabbits, or hamsters with the intermittent exposure protocol (MacEwen and Vemot 1983). No evidence of neurotoxicity was observed in rats exposed to ≤300 mg/m^3 Skydrol500B-4 intermittently for 6 or 13 weeks (Healy et al. 1992; Monsanto 1987a, 1987b, 1989). The intermittent protocol used by Siegel et al. (1965) produced no signs of neurotoxicity in rabbits or dogs at 50 mg/m^3 triaryl phosphate. It produced delayed peripheral neuropathy in chickens at 50 mg/m^3 but not at 25 mg/m^3.

No information was located regarding neurological effects in animals after chronic inhalation exposure to organophosphate ester hydraulic fluids.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding neurological effects in humans after inhalation exposure to polyalphaolefin hydraulic fluids.

In a series of acute lethality studies, lethargy and inactivity were noted in rats exposed for 4 hours to lethal concentrations of DTNSRDC N501 (6,430 mg/m^3) (MacEwen and Vemot 1983). Kyphosis was observed in rats exposed to 880-5,030 mg/m^3 of a polyalphaolefin hydraulic fluid designated as B85-174 (Kinkead et al. 1987b). Because of the uncertainty of whether the kyphosis is a neurological or muscular effect, this effect is discussed in both-the Musculoskeletal Effects and Neurological Effects sections. No other information was located on neurological effects in animals after inhalation exposure to polyalphaolefin hydraulic fluids.

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2.2.1.5 Reproductive Effects

Mineral Oil Hydraulic Fluids. No studies were located regarding reproductive effects in humans or animals after inhalation exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding reproductive effects in humans after inhalation exposure to organophosphate ester hydraulic fluids.

Testicular atrophy was observed upon gross necropsy after male rats were continuously exposed for 90 days to an aerosol concentration of 101 mg/m^3 Durad MP280, but not in rats exposed to 10.3 mg/m^3 (MacEwen and Vemot 1983). Testicular atrophy was not observed in male rats continuously exposed for 90 days to an aerosol concentration of 100 mg/m^3 Fyrquel 220 (MacEwen and Vemot 1983).

Male and female rats showed no treatment-related gross or histological reproductive tract alterations when exposed by inhalation 6 hours/day, 5 days/week for 3 weeks to a 990 mg/m^3 aerosol of cyclotriphosphazene (Kinkead et al. 1989a, 1990), or aerosol concentrations of Skydrol 500B-4 ≥300 mg/m^3, 6 hours/day, 5 days/week for 13 weeks (Healy et al. 1992; Monsanto 1987a, 1987b, 1989).

Likewise, no treatment-related gross reproductive tract alterations after intermediate-duration exposure were observed in male or female rabbits or in male hamsters continuously exposed to aerosols of Fyrquel220 at concentrations ≤100 mg/m^3 (MacEwen and Vemot 1983). Two male rabbits exposed for l-4 hours/day, 4-5 days/week, for 11-26 days to 2,000 mg/m^3 aerosol of Cellulube 220 (Carpenter et al. 1959) showed no histological evidence for effects on reproductive tissues. No acute or chronic inhalation studies examining reproductive effects in animals were located.

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

Polyalphaolefin Hydraulic Fluids. No studies were located regarding reproductive effects in humans or animals after inhalation exposure to polyalphaolefin hydraulic fluids.

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2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, or polyalphaolefin hydraulic fluids.

2.2.1.7 Genotoxic Effects

Mineral Oil Hydraulic Fluids. No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to organophosphate ester hydraulic fluids. Genotoxicity studies for organophosphate ester hydraulic fluids are discussed in Section 2.5.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to polyalphaolefin hydraulic fluids.

2.2.1.8 Cancer

Mineral Oil Hydraulic Fluids. Studies regarding cancer in humans or animals after inhalation exposure to mineral oil hydraulic fluids were limited to a single case-control study that examined associations between subjectively reported occupational exposure to petroleum-derived liquids and cancer at particular sites among 3,726 male cancer patients (Siemiatycki et al. 1987a). The study found no convincing associations between occupational exposure to hydraulic fluids and cancer at any site. This study is discussed in more detail in Section 2.2.3.8, because, while inhalation exposure was probable for the subject occupations, the authors reported that the exposure route was more often dermal contact.

No studies were located regarding cancer in animals after inhalation exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding cancer in humans or animals after inhalation exposure to organophosphate ester hydraulic fluids.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding cancer in humans or animals after inhalation exposure to polyalphaolefin hydraulic fluids.

2.2.2 Oral Exposure

The NOAEL and LOAEL values for each effect after oral exposure are shown in Tables 2-4,2-5, and 2-6 and plotted in Figures 2-4,2-5, and 2-6 for mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, and polyalphaolefin hydraulic fluids, respectively.

2.2.2.1 Death

Mineral Oil Hydraulic Fluids. A 14-month-old boy ingested ≈5-10 cc of automobile automatic transmission fluid thought to have been composed primarily (75-80%) of mineral oil (Perrot and Palmer 1992). The child developed pneumonia, pneumothorax (presence of gas in the pleural cavity), hemorrhaging in the intestines, and a distended abdomen and eventually died 4 weeks after ingestion. Postmortem examination revealed scattered subserosal hemorrhage in the small and large intestine and the omentum, as well as focal edema, hemorrhage, and lipoid/oil droplets in the lung, and proliferation of alveolar macrophages. The presence of lipoid/oil droplets in the lung suggest that the transmission fluid was aspirated. Additional information was not located on lethality of mineral oil hydraulic fluids in humans after oral exposure.

Several water-in-oil emulsion hydraulic fluids (Houghto-Safe 5047F, Sunsafe F, Pyroguard A-443, and Quintolubric 95830W) produced no deaths or clinical signs of toxicity at single gavage dosage levels of 5,000 mg/kg in rats observed for 14 days (Kinkead et al. 1987a, 1988). Single gavage doses of a U.S. military fluid designated as MIL-H-5606 at 4,500 mg/kg (5 mL/kg) also produced no deaths in rats observed for 14 days (Kinkead et al. 1985). Additional information on lethality of mineral oil hydraulic fluids in animals after oral exposure was not located. No studies showing LOAEL values for lethality are shown in Table 2-4 or Figure 2-4.

Table 2-4. Levels of Significant Exposure to Mineral Oil Hydraulic Fluids - Oral

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Fluid Identity
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	ACUTE EXPOSURE						
	Systemic						
1	Rat (Fischer- 344)	once (GO)	Bd Wt	5000			Kinkead et al. 1987a; Kinkead et al. 1988 Houghto-Safe 5047F
2	Rat (Sprague-Dawley)	once (GO)	Bd Wt	4500			Kinkead et al. 1985 MIL-H-5606
3	Rat (Fischer- 344)	once (GO)	Bd Wt	5000			Kinkead et al. 1987a; Kinkead et al. 1988 Pyroguard A-443
4	Rat (Fischer- 344)	once (GO)	Bd Wt	5000			Kinkead et al. 1987a; Kinkead et al. 1988 Quintolubric 95830W
5	Rat (Fischer- 344)	once (GO)	Bd Wt	5000			Kinkead et al. 1987a; Kinkead et al. 1988 Sunsafe F
	Neurological						
6	Chicken (Leghorn)	once (GO)		4500			Kinkead et al. 1985 MIL-H-5606

Table 2-4. Levels of Significant Exposure to Mineral Oil Hydraulic Fluids - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Fluid Identity
	INTERMEDIATE EXPOSURE						
	Systemic						
7	Rat (Fischer- 344)	26 d 5 d/wk (G)	Resp		1000M (granulomatous peribroncholitis & multifocal broncholar /alveolar pneumonia in 1 rat each)		Mattie et al. 1993 MIL-H-5606
			Gastro		1000M (focal gastritis with edema and necrosis in 2 animals)		
			Hemato		1000M (16% reduction in the percent lymphocytes)		
			Hepatic		1000M (32% increase in liver weights; 178% increase in peroxisomal beta-oxidation enzyme activity)		
			Renal		1000M (proximal tubule hyaline droplets, persistent diuresis [50-100% increase]; increases in protein content [100%] and protein/creatinine ratio [70%])		
			Bd Wt	1000 M			

[a]The number corresponds to entries in Figure 2-4.

Bd Wt = body weight; d = day(s); (G) = gavage, unspecified; Gastro = gastrological; (GO) = gavage-oil; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; once = a single dose or exposure; Resp = respiratory; wk = week(s)

Figure 2-4. Levels of Significant Exposure to Mineral Oil Hydraulic Fluids - Oral

Acute (≤14 days)

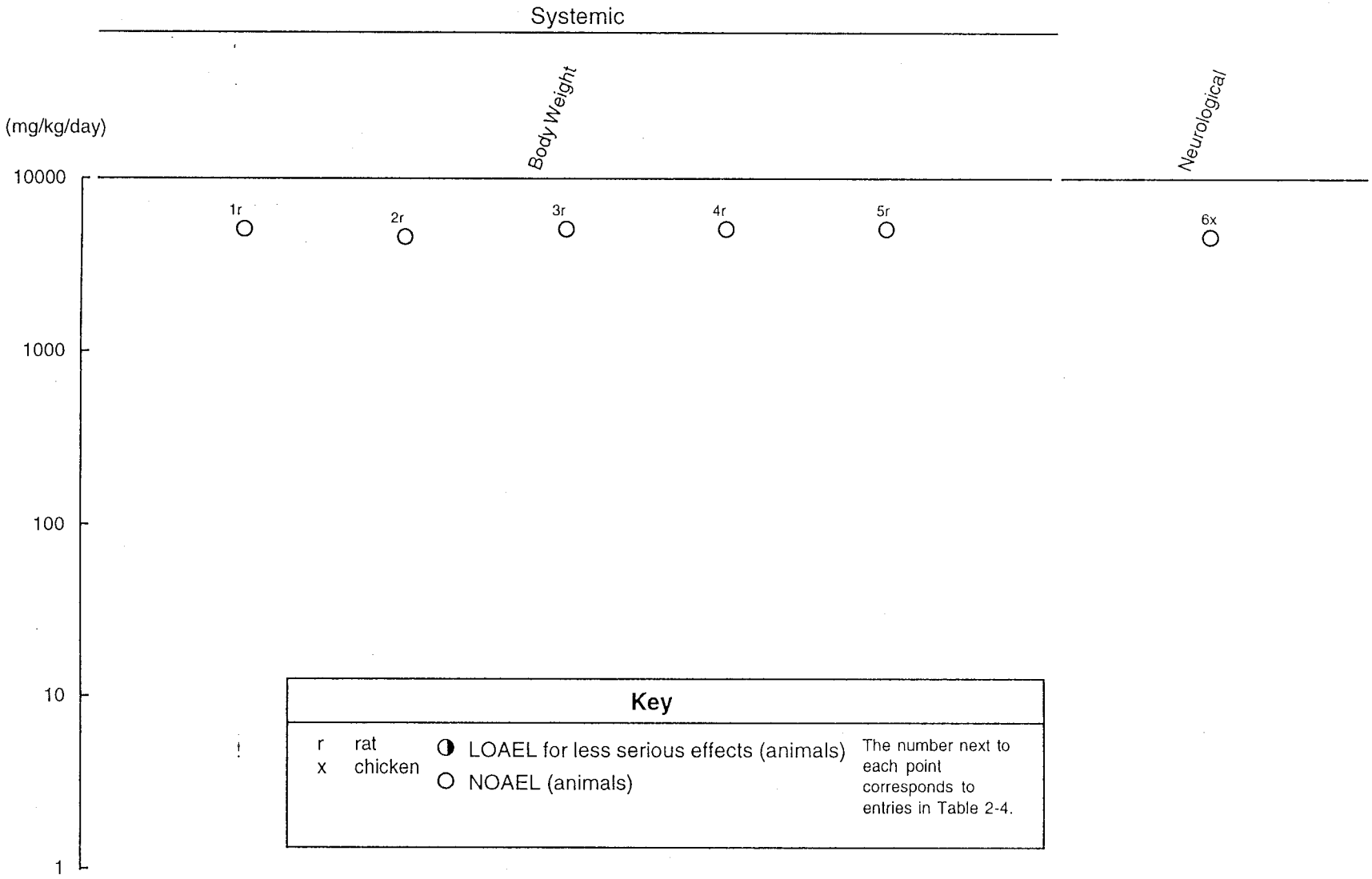


Figure 2-4. Levels of Significant Exposure to Mineral Oil Hydraulic Fluids - Oral (cont.)

Intermediate (15-364 days)

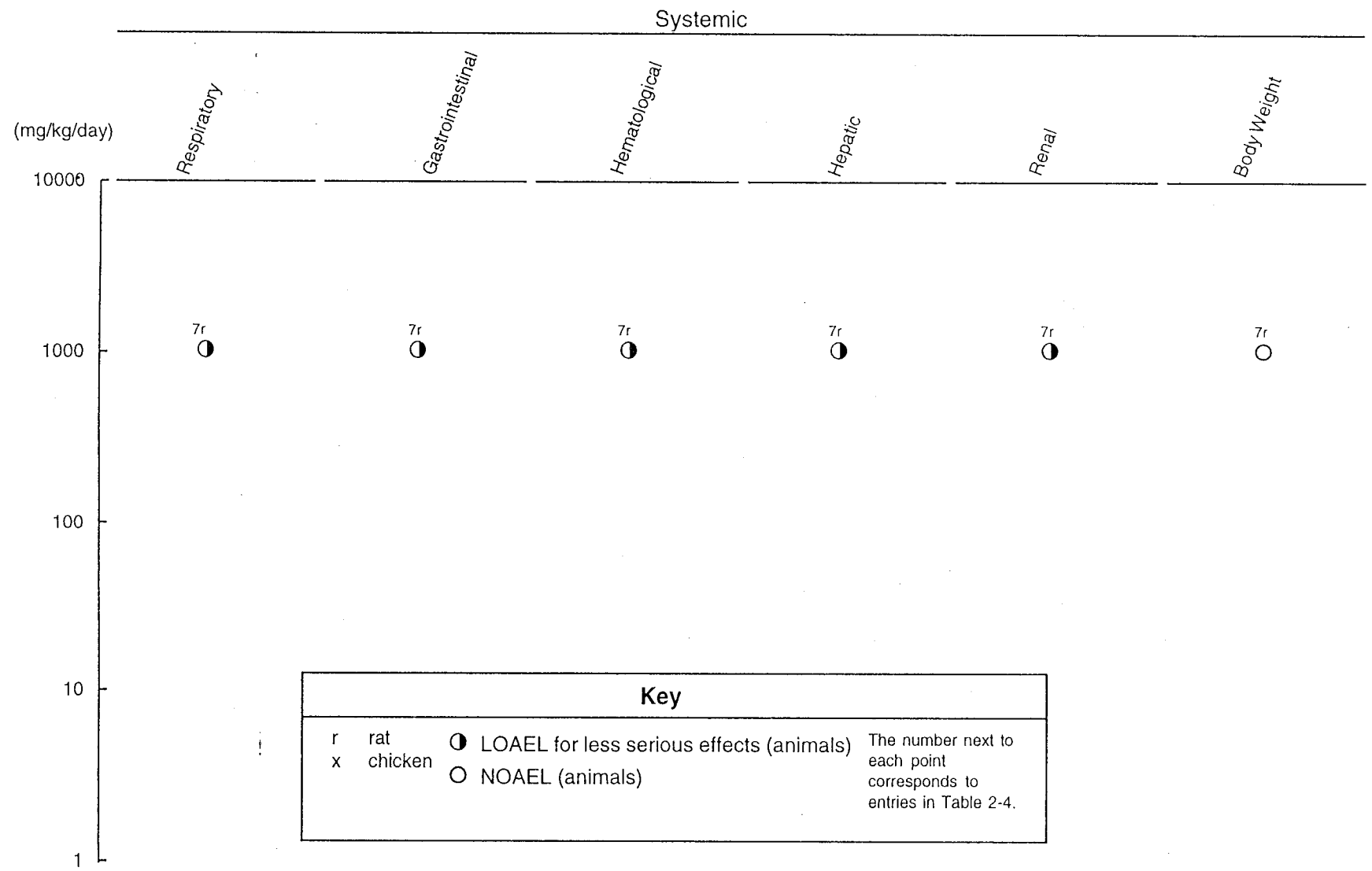


Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral

Key to[a] 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 Fluid Identity
	ACUTE EXPOSURE							
	Death							
1	Rat (Sprague-Dawley)	once (GO)				2400	(LD_{50})	Johannsen et al. 1977 DBPP
2	Rat (Wistar)	once (G)				34500	(3/10 died within 14 days)	FMC 1978a Pydraul 50E
3	Rat (Sprague-Dawley)	once (GO)				1400	(LD_{50})	Johannsen et al. 1977 TBP
4	Rat (Wistar)	Gd 7-17 1 x/d (GO)				800 F	(death in 5/5 by Gd 12 or 13)	Noda et al. 1994 TBP
5	Rat (Sprague-Dawley)	once (GO)				1000 F	(1/12 females died)	Healy et al. 1995 TNBP
6	Rabbit (New Zealand)	2-14 d (GO)				120	(1/2 died)	Carpenter et al. 1959 Cellulube 220
7	Rabbit (NS)	once (G)				7500	(4/5 died)	Dollahite and Pierce 1969 Cellulube 220
8	Cow (NS)	once (G)				7700	(1/1 died)	Dollahite and Pierce 1969 Cellulube 220
9	Cow (NS)	10 d 1 x/d (G)				500	(1/1 died)	Beck et al. 1977 Fyrquel 150

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
10	Cow (Hereford & Charolais)	once (G)				5000 (1/1 died)	Beck et al. 1977 Fyrquel 150
11	Chicken (NS)	once (C)				1863 F (LD_{50})	Carrington et al. 1989 DBPP
12	Chicken (White Leghorn)	5 d 1 x/d (GO)				300 F (2/4 died)	Stauffer Chemical 1971 Fyrquel 150
13	Chicken (Rhode Island Red x New Hampshire Red)	5 d 1 x/d (G)				5000 F (3/4 died)	FMC 1977a Fyrquel 220
14	Chicken (Leghorn)	once (G)				2559 F (LD_{50})	Monsanto 1987d Skydrol 500 B-4
15	Chicken (Leghorn)	once (G)				2594 F (LD_{50})	Monsanto 1987c Skydrol LD-4
16	Chicken (NS)	once (C)				1500 F (LD_{50})	Carrington et al. 1989 TBP
	Systemic						
17	Rat (Sprague-Dawley)	once (G)	Resp Ocular Bd Wt	 5000 5000	5000 (chromorhinorrhea)		FMC 1990a Durad 110
18	Rat (Sprague-Dawley)	once (G)	Resp Bd Wt	 5000	5000 (chromorhinorrhea)		FMC 1990g Durad 220B

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
19	Rat (Sprague-Dawley)	once (G)	Resp Bd Wt	 5000	5000 (chromorhinorrhea)		FMC 1990d Durad 300
20	Rat (Sprague-Dawley)	once (G)	Bd Wt	5000			FMC 1992a Durad 550B
21	Rat (Sprague-Dawley)	once (GO)	Resp Gastro Bd Wt	5775 	 5775 (diarrhea) 5775 (transient weight loss)		Gaworski et al. 1986 Durad MP280
22	Rat (Sprague-Dawley)	once (GO)	Resp Gastro Bd Wt	5750 5750	 5750 (diarrhea)		Gaworski et al. 1986; Kinkead et al. 1992a Fyrquel 220
23	Rat (Wistar)	Gd 7-17 1 x/d (GO)	Bd Wt	100 F	200 F (12% decreased maternal body weight)		Noda et al. 1994 TBP
24	Rat (Wistar)	Gd 7-17 1 x/d (GO)	Bd Wt	500 F			Noda et al. 1994 TBP

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
25	Rabbit (New Zealand)	2-14 d (GO)	Resp			120 (pulmonary atelectasis and bronchopneumonia)	Carpenter et al. 1959 Cellulube 220
			Cardio	480			
			Gastro			120 (moderate to severe diarrhea)	
			Hemato	480			
			Musc/skel	480			
			Hepatic	480			
			Renal	480			
			Endocr	480			
26	Rabbit (NS)	once (G)	Gastro	2000	5000 (diarrhea)		Dollahite and Pierce 1969 Cellulube 220
27	Cow (Hereford & Charolais)	once (G)	Resp			500 (rapid respiration)	Beck et al. 1977 Fyrquel 150
			Gastro			500 (abdominal pain, diarrhea)	
	Neurological						
28	Mouse (Swiss CD-1)	14 d (F)		1138		2275 (piloerection, tremors, and lethargy)	Chapin et al. 1988 TCP
29	Cow (NS)	once (G)				7700 (incoordination, demyelination and axonal swelling in peripheral nervous system, incr. cellularity in spinal nerve roots, vacuolation of large neurons in ventral motor nucleus and nucleus ruber)	Dollahite and Pierce 1969 Cellulube 220
30	Cow (Hereford & Charolais)	10 d (G)				500 (miosis, salivation, coma convulsion, decreased blood cholinesterase level)	Beck et al. 1977 Fyrquel 150

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
31	Cow (Hereford & Charolais)	once (G)				500	(miosis, salivation, coma, convulsions, decreased blood cholinesterase, axonal degeneration, paralysis)	Beck et al. 1977 Fyrquel 150
32	Goat (NS)	once (G)				5000	(anorexia, incoordination, paralysis, demyelination and swelling of axon cylinder, vacuolation in neurons of motor nucleus)	Dollahite and Pierce 1969 Cellulube 220
33	Chicken (New Hampshire Red)	5 d 1 x/d (GO)				60 F	(leg or wing weakness)	Carpenter et al. 1959 Cellulube 220
34	Chicken (New Hampshire Red)	5 d 1 x/d (GO)				240 F	(ataxia)	Carpenter et al. 1959 Cellulube 220
35	Chicken (NS)	once (G)		10000		20000	(paralysis in 2/7)	Dollahite and Pierce 1969 Cellulube 220
36	Chicken (New Hampshire)	5 d 1 x/d (GO)				240 F	(leg and wing weakness, paralysis)	Friess et al. 1959 Cellulube 220
37	Chicken (NS)	1-2 x (C)		1863 F				Carrington et al. 1989 DBPP

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Fluid Identity
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
38	Chicken (Leghorn)	5 d 1 x/d (GO)					240 F	(axonal degeneration and demyelination in peripheral nerves and spinal cord white matter)	Gaworski et al. 1986 Durad MP280
39	Chicken (White Leghorn)	5 d (GO)					240 F	(severe paralysis)	Stauffer Chemical 1971 Fyrquel 150
40	Chicken (Rhode Island Red x New Hampshire Red)	5 d (G)					5000 F	(paralysis)	FMC 1977a Fyrquel 220
41	Chicken (Leghorn)	5 d 1 x/d (GO)		420 F					Gaworski et al. 1986 Fyrquel 220
42	Chicken (White Leghorn)	once		2500 F	5000 F	(increased incidence of unspecified spinal cord lesions)	10000 F	(ataxia, increased incidence of unspecified spinal cord and peripheral nerve lesions)	Mortensen and Ladefoged 1992 Fyrquel EHC
43	Chicken (White Leghorn)	once (GO)					11350 F	(94% decrease in brain NTE, incoordination, inability to stand)	Stauffer Chemical 1980 Fyrquel EHC
44	Chicken (White Leghorn)	once (GO)		11.4 F	114 F	(13.4% inhibition of brain NTE)	1140 F	(56% inhibition of brain NTE)	Stauffer Chemical 1981 Fyrquel EHC
45	Chicken (White Leghorn)	2 x/21 d (GO)		370 F	11700 F	(motor incoordination)			Sprague et al. 1984 IPTPP

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Fluid Identity
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
46	Chicken (Leghorn)	5 d (GO)		420 F			Kinkead et al. 1989b MIL-H-19457B and MIL-H-19457C
47	Chicken (NS)	1-3 d 2 x (G)		20000 F			Monsanto 1979 Pydraul 29 ELT
48	Chicken (Rhode Island Red x New Hampshire Red)	4 d (G)		5000 F			FMC 1977b Pydraul 50E
49	Chicken (NS)	3 d 2 x/d (G)		20000 F			Monsanto 1979 Pydraul 50E
50	Chicken (NS)	3 d 2 x/d (G)		20000 F			Monsanto 1979 Pydraul 90E
51	Chicken (Hybrid white Leghorn)	2 x			5000 F (increased severity of unspecified peripheral nerve lesions)		Mortensen and Ladefoged 1992 Reofos 65
52	Chicken (NS)	once (G)			2559 F (inhibition of NTE [46%], brain AChE [18%])		Monsanto 1987d Skydrol 500 B-4
53	Chicken (Leghorn)	once (G)			2594 F (inhibition of NTE [29%] brain AChE [15%])		Monsanto 1987c Skydrol LD-4
54	Chicken (NS)	1-2 x (C)			5000 F (45% inhibition of brain AChE)		Carrington et al. 1989 TBEP

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Fluid Identity
					Less Serious (mg/kg/day)		Serious (mg/kg/day)	
55	Chicken (NS)	1-2 x (C)			1500 F	(salivation, diarrhea, and impaired respiration)		Carrington et al. 1989 TBP
	Reproductive							
56	Rabbit (New Zealand)	2-14 d (GO)		480 M				Carpenter et al. 1959 Cellulube 220
	Developmental							
57	Rat (COBS CD)	Gd 6-15 1 x/d (G)		3000				Robinson et al. 1986 Santicizer 141
58	Rat (COBS CD)	Gd 6-19 1 x/d (G)		3000				IRDC 1981 Santicizer 154
59	Rat (Wistar)	Gd 7-17 1 x/d (GO)		250	500	(increased incidence of rudimentary lumbar rib)		Noda et al. 1994 TBP

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
	INTERMEDIATE EXPOSURE						
	Death						
60	Rat (Fischer- 344)	26 d 5 d/wk 1 x/d (G)				1000 M (4/4 died)	Mattie et al. 1993 MIL-H-83306
61	Rat (Sprague-Dawley)	13 wk (GO)				100 (2/12 male and 1/12 female died)	Healy et al. 1995 TNBP
62	Chicken (Hybrid brown)	91-94 d (GO)				90 F (5/20 died)	FMC 1986 Durad 110
	Systemic						
63	Rat (Fischer- 344)	20, 40, 60 d 1 x/d (G)	Endocr		1700 (bilaterally enlarged adrenal glands, lipidosis in adrenal cortex of 18/18, vacuolization of cortex cytoplasm)		Latendresse et al. 1994a BTP
64	Rat (Fischer- 344)	106 d (GO)	Bd Wt		1000 (11-17% decreased body weight)		Latendresse et al. 1994b BTP

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
65	Rat (Sprague-Dawley)	91 d (F)	Hemato	50	250 (decreased erythrocyte count, hemoglobin and hematocrit levels)		Healy et al. 1991 DBPP
			Hepatic	50	250 (increased absolute and/or relative liver weights, decreased hepatocyte vacuolation and increased fatty accumulation)		
			Renal	5	50 (urinary bladder epithelial hyperplasia)		
			Bd Wt	250 M 50 F	250 F (15% decreased body weight)		
66	Rat (Fischer- 344)	26 d 5 d/wk 1 x/d (G)	Cardio	500 M			Mattie et al. 1993 MIL-H-83306
			Hemato		500M (decreased hemoglobin, mean cell hemoglobin, and mean cell hemoglobin concentration)		
			Hepatic		500M (increased smooth ER and relative and absolute liver weights; decreased BUN)		
			Renal		500M (diuresis, proteinuria)		
67	Rat (albino)	90 d (F)	Cardio	50			Monsanto 1979 Pydraul 90E
			Hemato	50			
			Hepatic	50			
			Renal	50			
			Bd Wt	50			

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Fluid Identity
					Less Serious (mg/kg/day)		Serious (mg/kg/day)	
68	Rat (Sprague-Dawley)	18 wk 5 d/wk 1 x/d (G)	Resp	350				Laham et al. 1985 TBP
			Cardio	350				
			Hemato	350				
			Hepatic	350				
			Renal		200	(diffuse hyperplasia of bladder epithelium)		
			Endocr	350 F				
			Bd Wt	200 M	350 M	(15% decrease in body weight)		
				350 F				
69	Rat (Wistar)	9 wk (F)	Hemato	250 M				Oishi et al. 1982 TBP
			Renal		250M	(increased blood urea nitrogen; increased relative kidney weight)		
			Bd Wt		250M	(11% decreased body weight)		
70	Rat (Fischer- 344)	20, 40, 60 d 1 x/d (GO)	Endocr		400	(bilaterally enlarged adrenal glands, lipidosis in adrenal cortex in 17/17, vacuolization of cortex cytoplasm)		Latendresse et al. 1994a TCP
71	Rat (Fischer- 344)	106 d (GO)	Bd Wt	400				Latendresse et al. 1994b TCP

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
72	Rat (Fischer- 344)	13 wk 7 d/wk (F)	Resp	770			NTP 1994 TCP
			Cardio	770			
			Gastro	770			
			Hepatic	770			
			Renal	430 M	750 M (renal papillary edema and/or necrosis)		
				230 F	430 F (renal papillary edema and/or necrosis)		
			Endocr		55 M (cytoplasmic vacuolization of the adrenal cortex) 65 F		
			Dermal	770			
			Bd Wt	220 M	430 M (11% decrease in body weight)	750 M (33% decrease in body weight)	
				220 F	430 F (11% decrease in body weight)		
73	Rat (Fischer- 344)	13 wk 5 d/wk (GO)	Resp	800			NTP 1994 TCP
			Cardio	800			
			Gastro	800			
			Hemato	800			
			Hepatic	800			
			Renal	800			
			Endocr		50 (cytoplasmic vacuolization of the adrenal cortex)		
			Dermal	800			
			Bd Wt	400 M	800 M (13% decreased body weight)		
				800 F			

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
74	Rat (Wistar)	9 wk (F)	Hemato		250 M (decr. erythrocyte counts and hemoglobin)		Oishi et al. 1982 TMP
			Hepatic	250 M			
			Renal	250 M			
			Bd Wt		250 M (12% decreased body weight)		
75	Rat (Wistar)	9 wk (F)	Hemato	250 M			Oishi et al. 1982 TOP
			Hepatic	250 M			
			Renal	250 M			
			Bd Wt	250 M			

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Fluid Identity
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
76	Mouse (B6C3F1)	13 wk 7 d/wk (F)	Resp	900 M 1050 F					NTP 1994 TCP
			Cardio	900 M 1050 F					
			Gastro	900 M 1050 F					
			Hemato	900 M 1050 F					
			Musc/skel	950 M 1050 F					
			Hepatic	45 M	110 M	(minimal papillary hyperplasia of the gallbladder mucosa in 4/10)			
				130 F	230 F	(mild papillary hyperplasia of the gallbladder mucosa in 10/10)			
			Renal	380 M	900 M	(renal tubule regeneration in 10/10)			
				1050 F					
			Endocr	45 M	110 M	(minimal to moderate cytoplasmic vacuolization of adrenal cortex)			
					65 F				
			Dermal	900 M 1050 F					
			Bd Wt	380 M	900 M	(18% decreased body weight)			
				230 F	530 F	(14% decreased body weight)	1050 F	20% decreased body weight)	

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Fluid Identity
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
77	Mouse (B6C3F1)	13 wk 5 d/wk (GO)	Resp	800					NTP 1994 TCP
			Cardio	800					
			Gastro	800					
			Hemato	800					
			Musc/skel	800					
			Hepatic	800					
			Renal	800					
			Endocr		50	(cytoplasmic vacuolization of the adrenal cortex)			
			Dermal	800					
			Bd Wt	200	400	(12-19% decreased body weight)	800 M	(24% decreased body weight)	
	Immunological/Lymphoreticular								
78	Rat (Fischer- 344)	16 d 5 d/wk (GO)		730	1450	(significantly decreased thymus weight)	2900	(necrosis of mandibular lymph node, spleen, and thymus)	NTP 1994 TCP
79	Rat (Fischer- 344)	13 wk 7 d/wk (F)		750 M 770 F					NTP 1994 TCP
80	Rat (Fischer- 344)	13 wk 5 d/wk (GO)		800					NTP 1994 TCP

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
81	Mouse (B6C3F1)	16 d 5 d/wk (GO)		730 M 1450 F	1450M (mild lymphoid depletion of thymus)	2900 (lymphoid depletion and necrosis of the spleen and thymus; necrosis of the mandibular lymph node)	NTP 1994 TCP
82	Mouse (B6C3F1)	13 wk 5 d/wk (GO)		800			NTP 1994 TCP
83	Mouse (B6C3F1)	13 wk 7 d/wk (F)		900 M 1050 F			NTP 1994 TCP
	Neurological						
84	Rat (Sprague-Dawley)	91 d (F)		250 M 50 F	250 F (decreased erythrocyte and brain aAChE levels)		Healy et al. 1991 DBPP
85	Rat (Fischer- 344)	13 wk 5 d/wk (GO)		800			NTP 1994 TCP
86	Rat (Fischer- 344)	13 wk 7 d/wk (F)		750 M 770 F			NTP 1994 TCP

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
87	Mouse (B6C3F1)	13 wk 7 d/wk (F)		180 M	380 M (decreased forelimb grip strength)	900 M (axonal degeneration in sciatic nerve and spinal cord, tremors)	NTP 1994 TCP
				230 F		530 F (decreased forelimb and hindlimb grip strength; axonal degeneration of the spinal cord and sciatic nerve)	
88	Mouse (B6C3F1)	13 wk 5 d/wk (GO)		50		100 (multifocal degeneration of the spinal cord and sciatic nerve)	NTP 1994 TCP
89	Chicken (NS)	28 d (GO)		444 F		1333 F (ataxia in 2/5)	FMC 1986 Durad 110
90	Chicken (Warren S.S.L)	91-94 d (GO)		20 F		90 F (ataxia in 4/20, axonal damage in spinal cord and peripheral nerves, stumbling, weak limb movements)	FMC 1986 Durad 110
91	Chicken (G. gallus)	10 wk 5 d/wk 1 x/d (GO)			10 F (depression of brain and spinal cord neurotoxic esterase activity)	60 F (ataxia, axonal degeneration)	Freudenthal et al. 1993 TCP
	Reproductive						
92	Rat (Fischer- 344)	20, 40, 60 d 1 x/d (G)		2800 M	1700 F (lipidosis in ovarian interstitial cells of 9/9)		Latendresse et al. 1994a BTP

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
93	Rat (Fischer- 344)	98 d (GO)				600 (decreased number of litters per fertile pair)	Latendresse et al. 1994b BTP
94	Rat (Fischer- 344)	106 d (GO)				1000 M (decreased fertility index) 1000 F (decreased mating and fertility indices, abnormal estrous cycle, decreased uterine weight)	Latendresse et al. 1994b BTP
95	Rat (Albino)	90 d (F)		50			Monsanto 1979 Pydraul 90E
96	Rat (Long- Evans)	66 d 1 x/d (GO)				100 M (increased abnormal sperm morphology and necrosis of seminiferous tubules) 200 F (decreased fertility; vacuolar cytoplasmic alteration of ovarian interstitial cells; increased follicular and luteal activity)	Carlton et al. 1987 TCP
97	Rat (Fischer- 344)	20, 40, 60 d 1 x/d (GO)			400 F (lipidosis in ovarian interstitial cells of 8/8, ovarian interstitial cell hypertrophy) 400M (testicular degeneration in 9/9; decreased testicular weight)		Latendresse et al. 1994a TCP
98	Rat (Fischer- 344)	106 d (GO)				400 M (100% infertility, decreased testicular and epididymal weights) 400 F (increased ovarian weight)	Latendresse et al. 1994b TCP

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
99	Rat (Fischer- 344)	98 d (GO)				400 (decreased fertility index, number of litters per fertile pair, and number of live pups per litter)	Latendresse et al. 1994b TCP
100	Rat (Fischer- 344)	13 wk 7 d/wk (F)		220 M	430 M (significantly decreased absolute and relative testis weight and small testes; atrophy of the seminiferous tubules) 65 F (hypertrophy & inflammation of ovarian interstitial cells)		NTP 1994 TCP
101	Rat (Fischer- 344)	13 wk 5 d/wk (GO)		200 M	400 M (atrophy of the seminiferous tubules) 50 F (ovarian interstitial cell hypertrophy)		NTP 1994 TCP
102	Mouse (Swiss CD-1)	25 wk (F)				250 (reduced number and proportion of live pups per litter and decreased fertility index) 250 M (decreased sperm motility and concentration, increased percentage of abnormal sperm, atrophy of the seminiferous tubules, decreased fertility index)	Chapin et al. 1988 TCP
103	Mouse (Swiss CD-1)	105 d (F)		62.5		124 (incr. number of dead pups and decr. number of live pups per litter, decr. number of litters)	Chapin et al. 1988 TCP

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
104	Mouse (B6C3F1)	13 wk 5 d/wk (GO)		200 M	400 M (seminiferous tubule atrophy in 10/10) 50 F (ovarian interstitial cell hypertrophy in 9/10)		NTP 1994 TCP
105	Mouse (B6C3F1)	13 wk 7 d/wk (F)		900 M 230 F	530 F (increased cytoplasmic vacuolization in ovarian interstitial cells)		NTP 1994 TCP
CHRONIC EXPOSURE							
Systemic							
106	Rat (Sprague-Dawley)	24 mo (F)	Hemato	143.3 M 181.5 F			FMC 1994a TBP
			Renal	8.9 M	32.5 M (epithelial hyperplasia and papilloma of urinary bladder)		
				11.6 F	42 F (epithelial hyperplasia and papilloma of urinary bladder)		
			Bd Wt	32.5 M	143.3 M (19% decreased body weight)		
				11.6 F	42 F (12% decreased body weight)	181.5 F (20% decreased body weight)	

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
107	Rat (Fischer- 344)	104 wk 7 d/wk (F)	Resp	13 M 15 F			NTP 1994 TCP
			Cardio	13 M 15 F			
			Gastro	13 M 15 F			
			Hemato	13 M 15 F			
			Musc/skel	13 M 15 F			
			Hepatic	13 M 15 F			
			Renal	13 M 15 F			
			Endocr	13 M 7 F	15 F (cytoplasmic vacuolization of the adrenal cortex in 36/50)		
			Dermal	13 M 15 F			
			Bd Wt	13 M 15 F			

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Fluid Identity
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
108	Mouse (B6C3F1)	105 wk 7 d/wk (F)	Resp	27 M 37 F			NTP 1994 TCP
			Cardio	27 M 37 F			
			Gastro	27 M 37 F			
			Hemato	27 M 37 F			
			Musc/skel	27 M 37 F			
			Hepatic	7 M 37 F	13M (increased incidences of clear cell foci, fatty change, and ceroid pigmentation)		
			Renal	27 M 37 F			
			Endocr		7M (ceroid pigmentation of the adrenal cortex: minimal to mild) 8 F (ceroid pigmentation of the adrenal cortex: moderate to marked)		
			Dermal	27 M 37 F			
			Bd Wt	27 M 37 F			
Immunological/Lymphoreticular							
109	Rat (Fischer- 344)	104 wk 7 d/wk (F)		13 M 15 F			NTP 1994 TCP

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
110	Mouse (B6C3F1)	105 wk 7 d/wk (F)		27 M 37 F			NTP 1994 TCP
	Neurological						
111	Rat (Fischer- 344)	104 wk 7 d/wk (F)		13 M 15 F			NTP 1994 TCP
112	Mouse (B6C3F1)	105 wk 7 d/wk (F)		27 M 37 F			NTP 1994 TCP
	Reproductive						
113	Rat (Fischer- 344)	104 wk 7 d/wk (F)		13 M 7 F	15 F (ovarian interstitial cell hyperplasia)		NTP 1994 TCP

Table 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Fluid Identity
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
114	Mouse (B6C3F1)	105 wk 7 d/wk (F)		27 M 37 F			NTP 1994 TCP

[a]The number corresponds to entries in Figure 2-5.

AChE = acetylcholinesterase; Bd Wt = body weight; BTP = butylated triphenyl phospate; BUN = blood urea nitrogen; (C) = capsule; Cardio = cardiovascular; d = day(s); decr. = decreased; DBPP = dibutylated phenyl phosphate; 2EDP = 2-ethylhexyl diphenyl phosphate; Endocr = endocrine; F = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GI) = gastric intubation; (GO) = gavage in oil; Hemato = hematological; incr. = increased; IPTPP = isopropyl triphenyl phosphate; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; MCV = mean corpuscular volume; MCHC = mean corpuscular hemoglobin concentration; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; NTE = neurotoxic esterase; RBC = red blood cell; Resp = respiratory; TBEP = tributoxyethyl phosphate; TBP = tributyl phosphate; TMP = trimethyl phosphate; TNBP = tri-n-butyl phosphate; TOP = trioctyl phosphate; wk = week(s); x = times; yr = year(s).

Figure 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Oral

Acute (≤14 days)

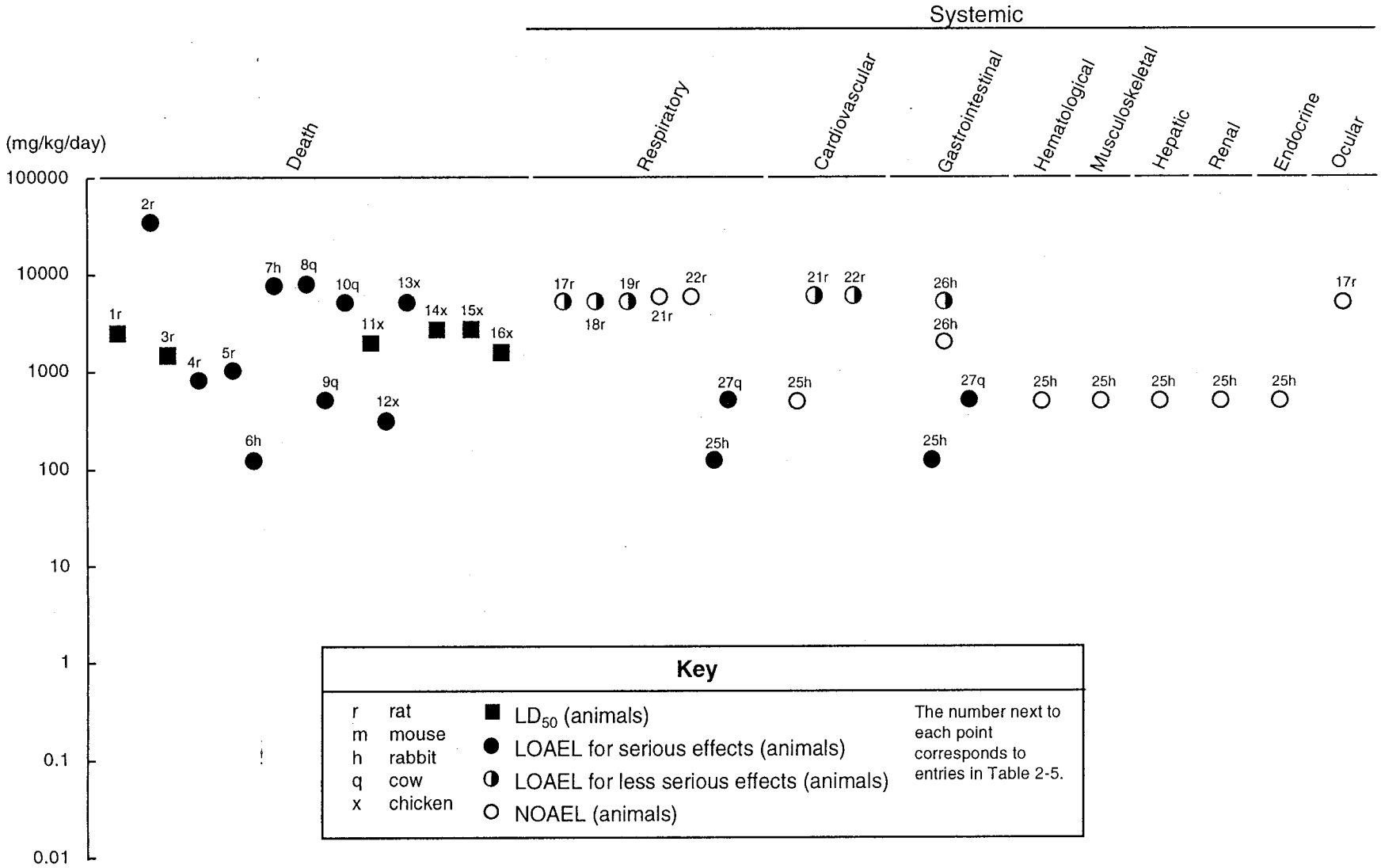


Figure 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids Oral (cont.)

(Acute (≤14 days)

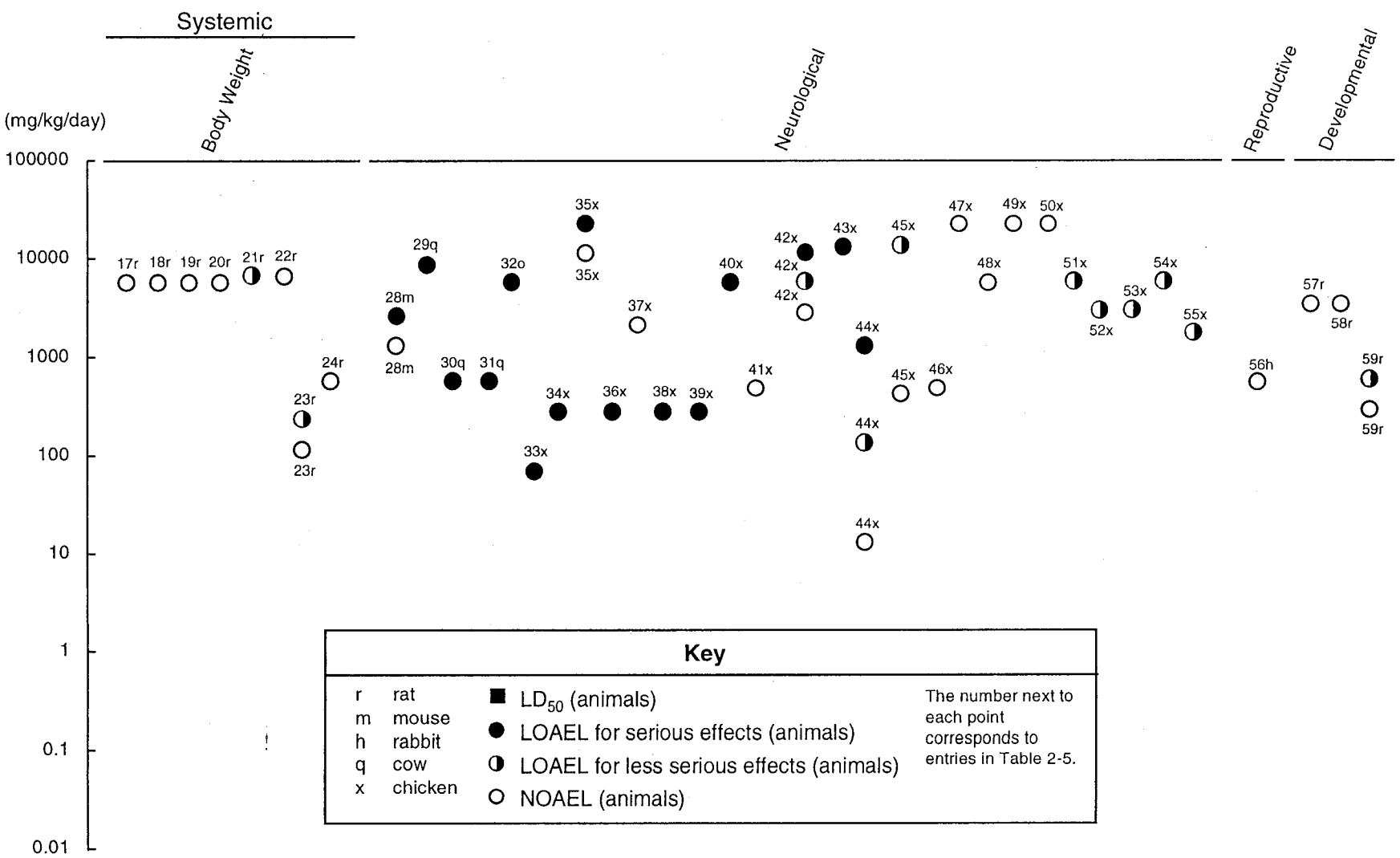


Figure 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids Oral (cont.)

Intermediate (15-364 days)

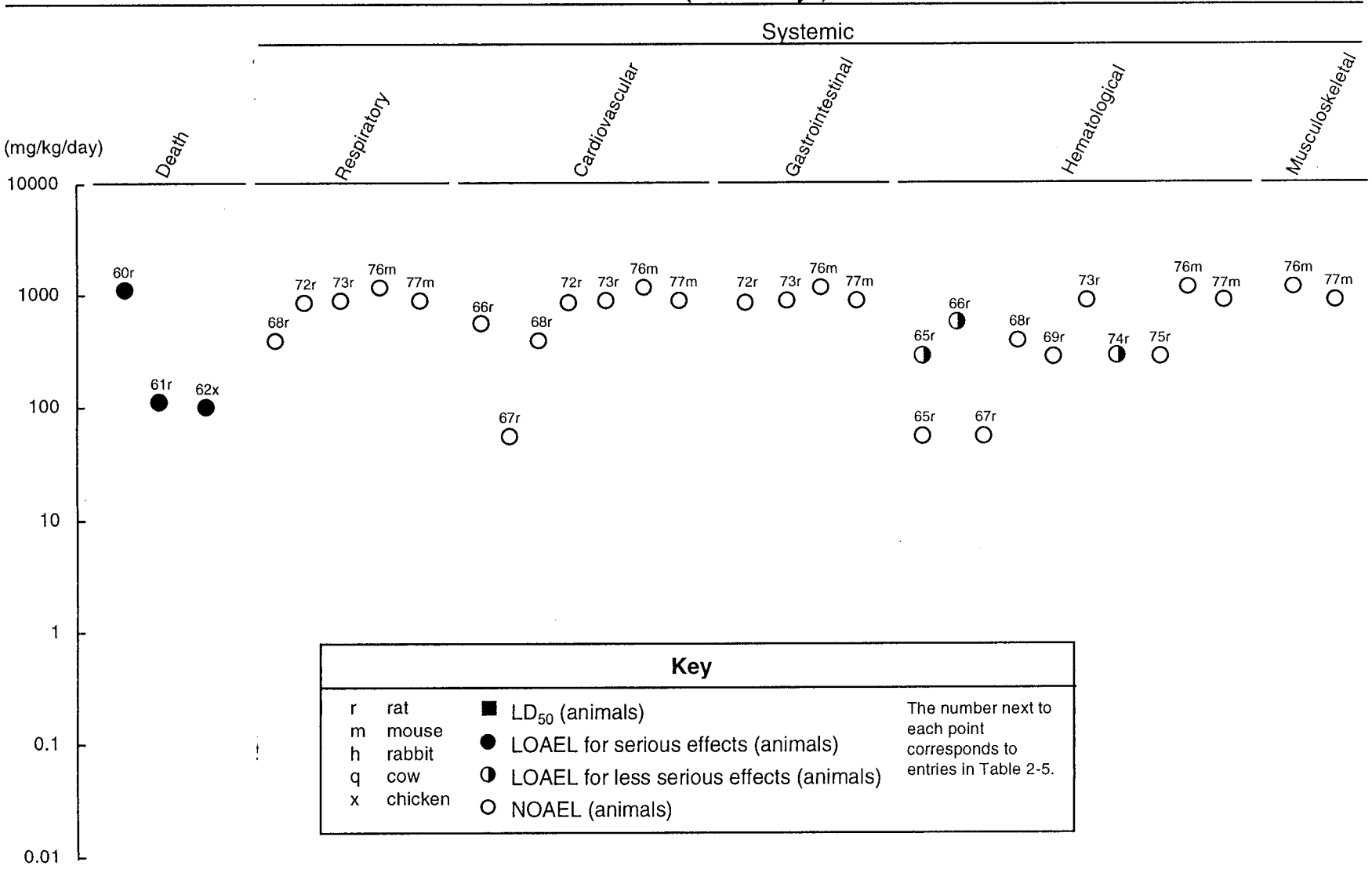


Figure 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids Oral (cont.)

Intermediate (15-364 days)

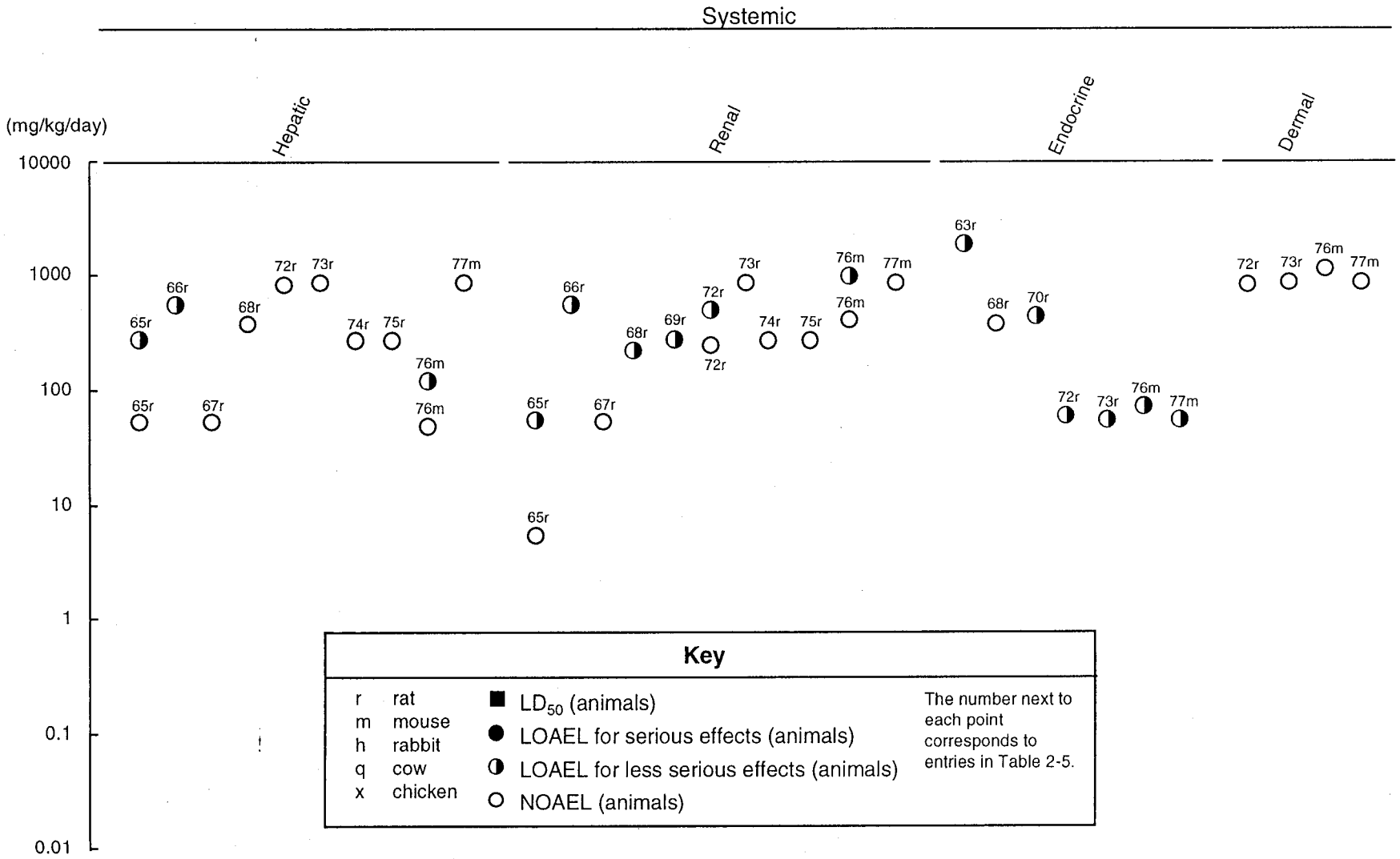


Figure 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids Oral (cont.)

Intermediate (15-364 days)

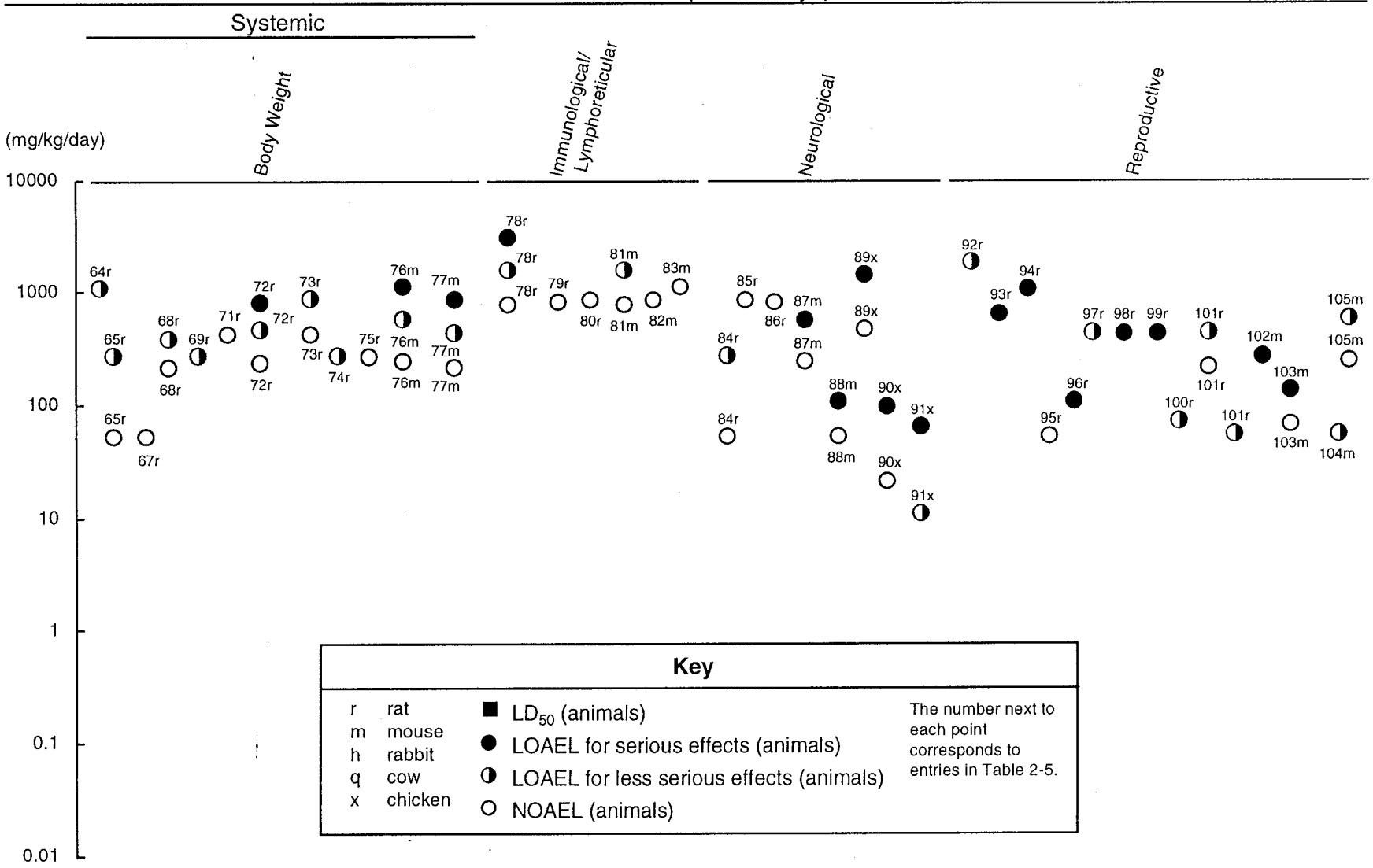


Figure 2-5. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids Oral (cont.)

Chronic (≥365 days)

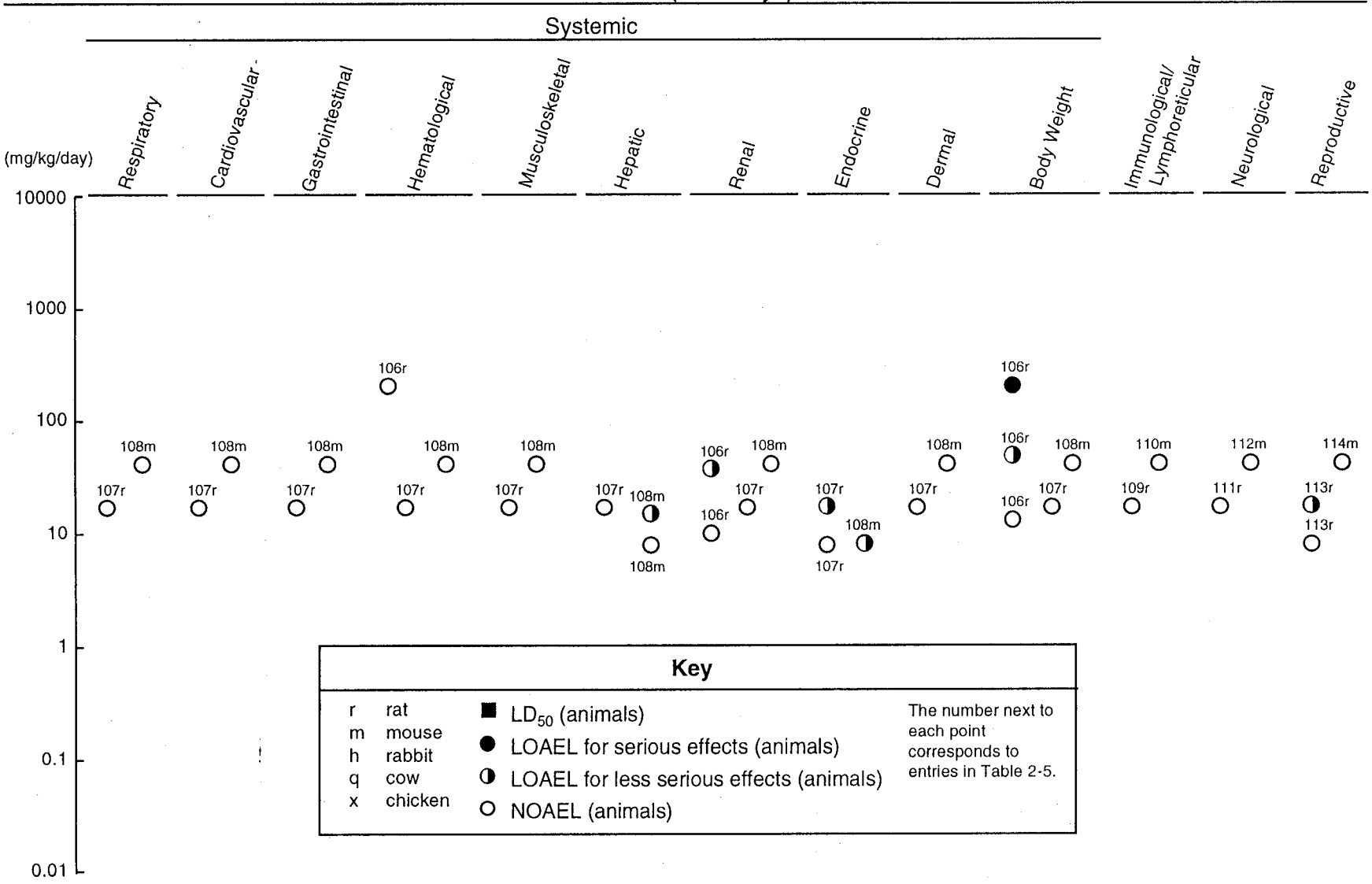


Table 2-6. Levels of Significant Exposure to Polyalphaolefin Hydraulic Fluids - Oral

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Fluid Identity
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	ACUTE EXPOSURE						
	Systemic						
1	Rat (Sprague-Dawley)	once (GO)	Bd Wt	5000			Kinkead et al. 1987b (B85-174)
2	Rat (Sprague-Dawley)	once (G)	Bd Wt	4250			MacEwen and Vernot 1983 (DTNSRDC N517)
3	Rat (Sprague-Dawley)	once (G)	Bd Wt	4250			MacEwen and Vernot 1983 (DTNSRDC N518)
4	Rat (Sprague-Dawley)	once (G)	Bd Wt	4250			MacEwen and Vernot 1983 (DTNSRDC N448)
5	Rat (Sprague-Dawley)	once (G)	Bd Wt	4250			MacEwen and Vernot 1983 (DTNSRDC N501)
6	Rat (Sprague-Dawley)	once (G)	Bd Wt	4250			MacEwen and Vernot 1983 (DTNSRDC N525)
7	Rat (Sprague-Dawley)	once (G)	Bd Wt	4250			MacEwen and Vernot 1983 (DTNSRDC N527)
8	Rat (Sprague-Dawley)	once (GO)	Bd Wt	4250			Kinkead et al. 1985 (MIL-H-83282)
9	Rat (Sprague-Dawley)	once (G)	Bd Wt	5000			Kinkead et al. 1992b (MIL-H-83282LT)

Table 2-6. Levels of Significant Exposure to Polyalphaolefin Hydraulic Fluids - Oral (continued)

Key to[a] 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 Fluid Identity
	Neurological						
10	Rat (Fischer- 344)	once (G)		5000			Kinkead et al. 1992b (MIL-H-83282LT)
11	Chicken (Leghorn)	once (GO)		6375 F			Kinkead et al. 1985 (MIL-H-83282)
	INTERMEDIATE EXPOSURE						
	Systemic						
12	Rat (Fischer- 344)	4 wk 5 d/wk 1 x/d (G)	Hemato	1000 M			Mattie et al. 1993 MIL-H-83282
			Hepatic		1000M (131% increase in peroxisomal oxidation rate; increase of 75 IU/L in alkaline phosphatase)		
			Renal		1000M (130% increase in urinary protein to creatinine ratio)		
			Bd Wt	1000 M			
13	Rat (Fischer- 344)	4 wk 5 d/wk 1 x/d (G)	Cardio	1000			Mattie et al. 1993 MIL-H-83282LT
			Hemato		1000M (47% increase in WBC; reductions, ~ 10%, in hemoglobin and mean cell hemoglobin concentration; anemia)		
			Hepatic		1000M (164% increase in peroxisomal oxidation rate)		
			Renal		1000M (diuresis)		
			Bd Wt	1000 M			

Table 2-6. Levels of Significant Exposure to Polyalphaolefin Hydraulic Fluids - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Fluid Identity
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	Immunological/Lymphoreticular						
14	Rat (Fischer- 344)	4 wk 5 d/wk 1 x/d (G)		1000			Mattie et al. 1993 MIL-H-83282
15	Rat (Fischer- 344)	4 wk 5 d/wk 1 x/d (G)		1000			Mattie et al. 1993 (MIL-H-83282LT)

[a]The number corresponds to entries in Figure 2-6.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = female; Hemato = hematological; (G) = gavage, unspecified; (GO) = gavage-oil; LOAEL = lowest-observed-adverse-effect-level; M = male; NOAEL = no-observed-adverse-effect level; once = a single dose or exposure; WBC = white blood cells; wk = week(s); x = times.

Figure 2-6. Levels of Significant Exposure to Polyalphaolefin Hydraulic Fluids - Oral

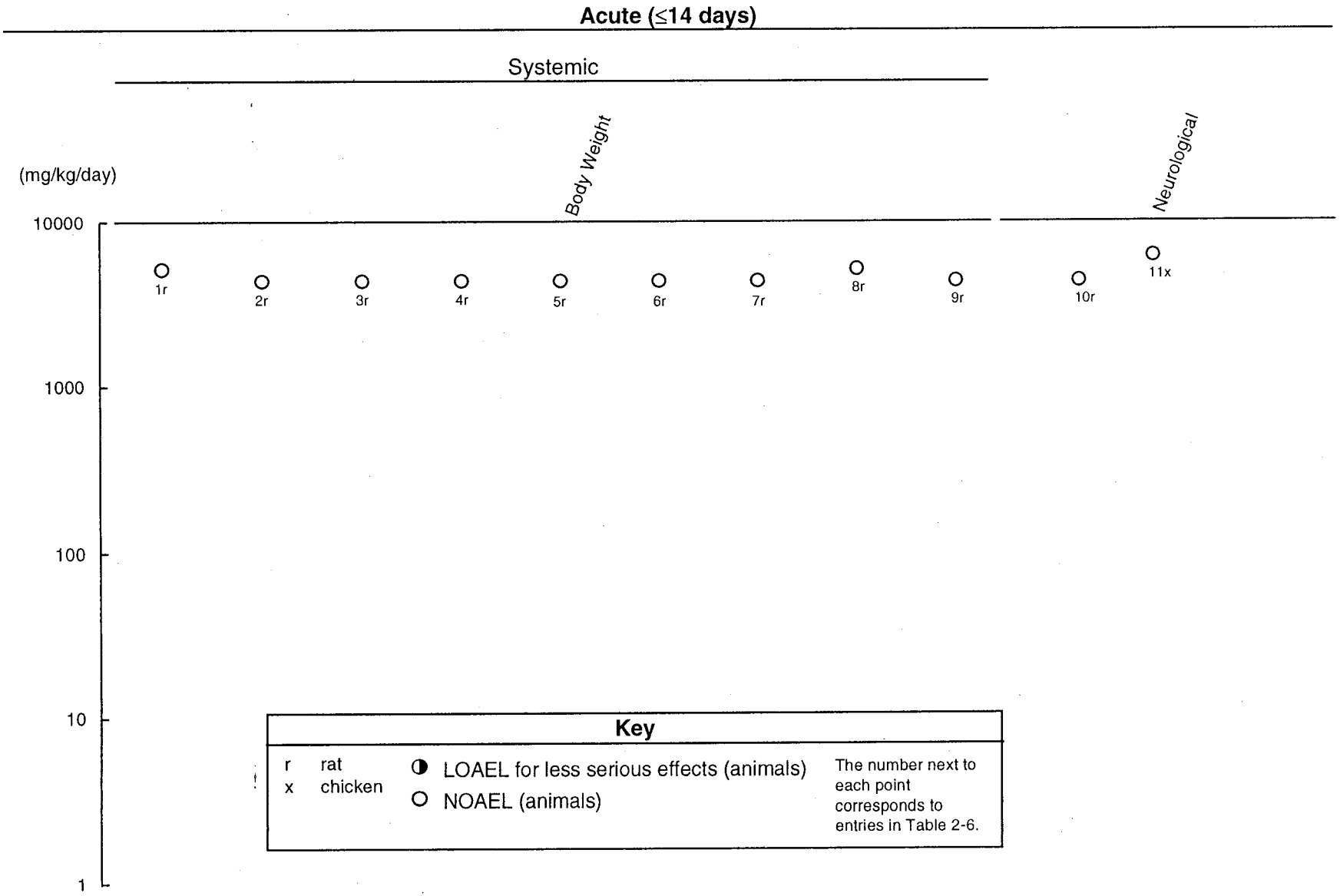
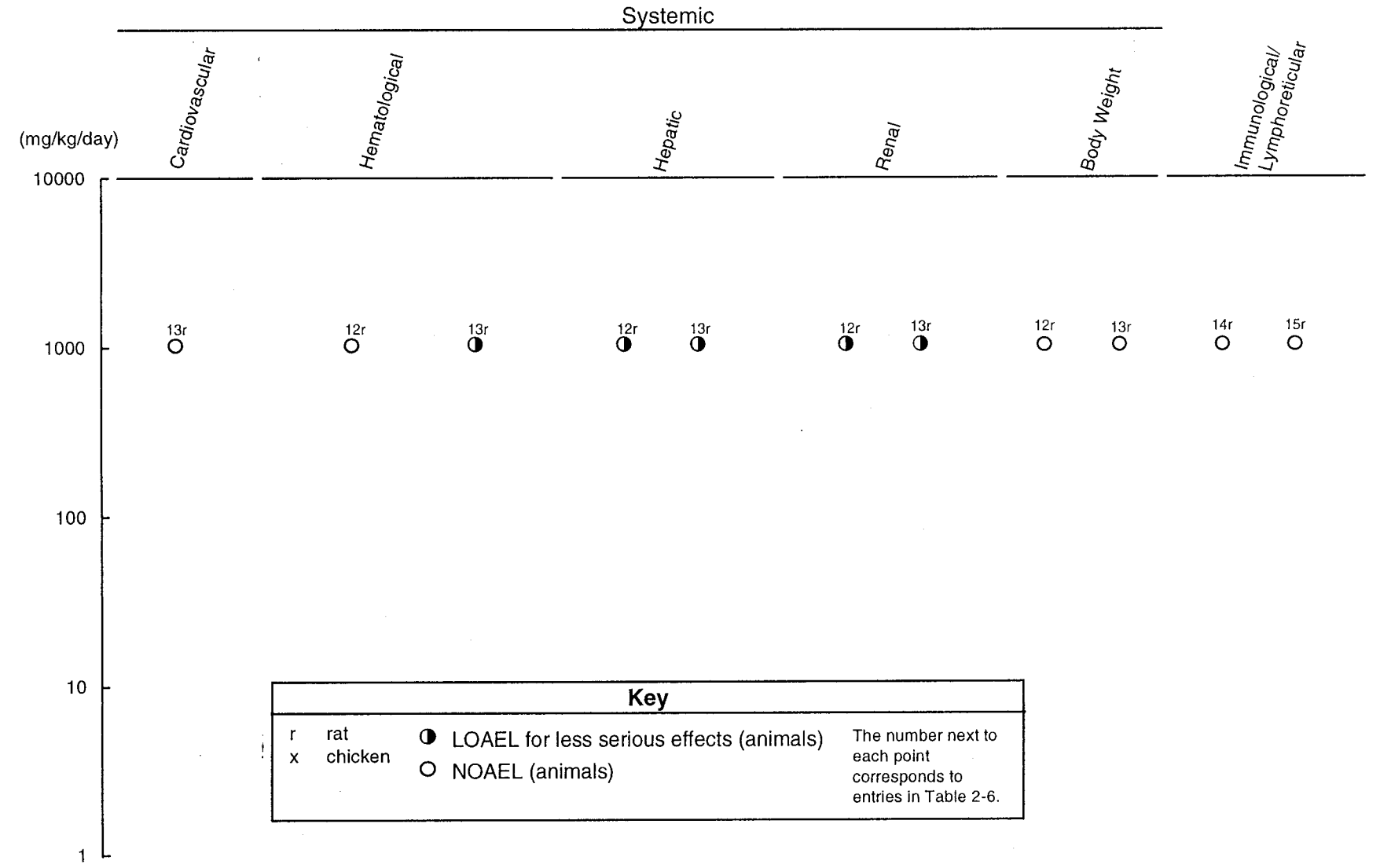


Figure 2-6. Levels of Significant Exposure to Polyalphaolefin Hydraulic Fluids - Oral (cont.)

Intermediate (15-364 days)



2. HEALTH EFFECTS

Organophosphate Ester Hydraulic Fluids. Reports of organophosphate poisonings in the United States, India, and South Africa date back to the 1930s when tri-*ortho*-cresyl phosphate was either inadvertently mixed with cooking oils or was an adulterant of an alcohol-containing extract, Jamaica Ginger (Goldstein et al. 1988). Few deaths are reported, but polyneuritis and paralysis are common to these outbreaks.

Acute oral exposure to several organophosphate ester hydraulic fluids produced deaths in rabbits, chickens, and cows. The deaths were associated with severe cholinergic symptoms or symptoms of organophosphorus induced delayed neuropathy (OPIDN). (See Section 2.2.2.4 for further details on the neurological effects.)

Single oral gavage doses of several organophosphate ester hydraulic fluids produced deaths in rats. LD_{50} values are reported for rats at >8,400 mg/kg for triaryl phosphates, 2,400 mg/kg for dibutyl phenyl phosphate, and 1,400 mg/kg for tributyl phosphate (Johannsen et al. 1977). No deaths were reported for rats at the highest administered dosage levels which were: Durads 300, 550B, 116, and 220B, 5,000 mg/kg (FMC 1990a); Durad MP280,5,775 mg/kg (Gaworski et al. 1986); and Cellulube 220 (two rats tested), 20,000 mg/kg (Dollahite and Pierce 1969). Single gavage doses of 34,500 mg/kg Pydraul 50E produced deaths in 3 of 10 rats from unspecified causes, but a dosage level of 28,750 mg/kg produced no deaths (FMC 1978a). No deaths were reported in rats orally exposed to a cyclotriphosphazene-based fluid at ≤5,000 mg/kg (Kinkead et al. 1992c; MacEwen and Vemot 1985).

Cellulube 220 produced deaths (including animals killed due to morbidity) associated with severe cholinergic symptoms and paralysis that developed within 5 days in four of five rabbits after administration of single doses of 7,500 mg/kg, but no deaths were produced after two rabbits received doses of 6,000 mg/kg (Dollahite and Pierce 1969). Lethal cholinergic toxicity after 6 days was observed in one of two rabbits exposed daily to 120 mg/kg/day of Cellulube 220 for 2-14 days (Carpenter et al. 1959).

The actual composition of the Cellulube 220 was not reported in either the Dollahite or Carpenter studies, so the large difference in doses causing death can not be explained. Deaths were also reported in 5 of 5 pregnant Wistar rats after 5-6 daily doses of 800 mg/kg tributyl phosphate beginning on gestation day 7 (Noda et al. 1994).

The acute oral LD_{50} values for Skydrol 500B-4, Skydrol LD-4, tributyl phosphate, and dibutyl phenyl phosphate in chickens were 2, 559, 2, 594, 1,500 or 1,800, and <2,000 mg/kg, respectively; deaths occurred

2. HEALTH EFFECTS

within 1-3 days with severe cholinergic symptoms (Carrington et al. 1989; Johannsen et al. 1977; Monsanto 1987c, 1987d). Lethal single gavage doses of 300 and 5,000 mg/kg were associated with severe neurotoxicity (paralysis, and inability to stand) in chickens treated with Fyrquel 150 (Stauffer Chemical Co. 1971) and Fyrquel 220 (FMC 1977a), respectively.

A single gavage dose of 5,000 mg/kg Fyrquel 150 produced lethal cholinergic symptoms in a calf; dosage levels of 500 and 1,000 mg/kg also produced cholinergic signs in adult cows. Death resulted from paralysis about 20 days after dosing (Beck et al. 1977). A calf died 30 days after a single dose of 7,700 mg/kg Cellulube 220; decreased erythrocyte acetylcholinesterase was observed (time of onset not reported) and axonal degeneration and demyelination in the peripheral and central nervous systems were observed beginning 19 days after dosing (Dollahite and Pierce 1969).

Intermediate-duration oral exposure to Durad 110 produced deaths in chickens associated with the delayed development of neuropathy at dosage levels of 4,000 mg/kg/day in a 28-day study and 90 mg/kg/day in a 90-day study (FMC 1986). At 100 mg/kg/day over a 13-week period, 2 of 12 male and 1 of 12 female rats died with exposure to tri-n-butyl phosphate (Healy et al. 1995). Dietary administration of Pydraul 90E for 90 days providing daily doses of 50 mg/kg/day produced no chemical-related deaths in rats (Monsanto 1979). An organophosphate ester hydraulic fluid designated MIL-H-83306 also caused death in 4 of 4 rats exposed by gavage to 1,000 mg/kg over a 26-day period (Mattie et al. 1993).

Gavage exposure to 2,900 mg/kg/day tricresyl phosphate for 16 days, 5 days a week, resulted in death in 5 of 10 male and 7 of 10 female Fischer 344 rats (NTP 1994). Deaths occurred in 5 of 10 male and 10 of 10 female $B_6C_3F_1$ mice at 1,450 mg/kg/day in a parallel study. No deaths occurred in rats in 13-week feeding (≤770 mg/kg/day) or gavage studies (5 days a week, 5 800 mg/kg/day) or in 2-year feeding studies at ≤15 mg/kg/day (NTP 1994). Similar results were obtained in mice where the highest doses were 1,050 mg/kg/day (13-week feeding), 800 mg/kg/day (13-week gavage), and 37 mg/kg/day (2-year feeding).

All LOAEL values for each reliable study for death in each species and duration category are recorded in Table 2-5 and plotted in Figure 2-5.

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Polyalphaolefin Hydraulic Fluids. No studies were located regarding death in humans after oral exposure to polyalphaolefin hydraulic fluids.

A U.S. military polyalphaolefin hydraulic fluid, MIL-H-83282LT, produced no deaths in adult leghorn chickens when two gavage doses of 5,000 mg/kg were administered separated by 21 days; a 21 -day observation period followed the second dose administration (Kinkead et al. 1992b). Single gavage 5 ml/kg (≈4,250 mg/kg) doses of another U.S. military fluid, MIL-H-83282, produced no deaths in rats within 14 days of dosing (Kinkead et al. 1985). No deaths occurred within 14 days of dosing in other groups of rats treated with one of several other U.S. military polyalphaolefin hydraulic fluids (designated as B85-174 and DTNSRDC Nos. N448, N501, N5 17, N5 18, N525, and N527) at single gavage dosage levels of 5 mL/kg (≈4,250 mg/kg) or 5,000 mg/kg (Kinkead et al. 1987b; MacEwen and Vemot 1983). No other information was located regarding deaths in animals after oral exposure to polyalphaolefin hydraulic fluids.

2.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Tables 2-4,2-5, and 2-6 and are plotted in Figures 2-4,2-5, and 2-6 for mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, and polyalphaolefin hydraulic fluids, respectively. Because of the uncertainty on whether chickens are a good model for human systemic effects (respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, and ocular), these data are not listed in the LSE tables or figures. However, chickens have been shown to be sensitive models for neurotoxicity, and data from chickens are included in the LSE tables and figures. Some of the systemic effects resulting from oral exposure to the organophosphate ester hydraulic fluids are most likely secondary to their anticholinesterase activity.

Respiratory Effects.

Mineral Oil Hydraulic Fluids. Lipoid pneumonia with marked interstitial pneumonitis and pulmonary fibrosis was observed in a child accidentally ingesting a lethal dose of automotive transmission fluid (Perrot and Palmer 1992). Although the exact composition of the hydraulic fluid was not reported, it is assumed to be a mineral oil hydraulic fluid because automotive transmission fluids typically contain 75-80% mineral oil. The presence of lipoid/oil droplets in the lungs suggested that some of the hydraulic fluid was aspirated.

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Granulomatous perbroncholitis (1 of 4) and multifocal bronchiolar/alveolar pneumonia (1 of 4) were noted in rats orally exposed to 1,000 mg/kg/day MIL-H-5606 for 26 days (Mattie et al. 1993). It is uncertain if these effects were treatment related.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding respiratory effects in humans after oral exposure to organophosphate ester hydraulic fluids.

A number of respiratory effects have been observed in animals acutely exposed to organophosphate ester hydraulic fluids by the oral route. Respiratory effects shortly after exposure to organophosphate ester hydraulic fluids may be due to acetylcholinesterase inhibition (see Neurological Effects sections for details). Rapid respirations were observed shortly after cows received a 500 mg/kg dose of Fyrquel 150 (Beck et al. 1977). In addition to the acetylcholinesterase inhibition-related effects, histological alterations have been observed. Bronchopneumonia and pulmonary atelectasis were observed in rabbits exposed to 120 mg/kg of Cellulube 220 (Carpenter et al. 1959), and emphysema, intralobular fibrosis, rapid respiration, and coughing were observed in cows exposed to Fyrquel 150 contaminated grass (Beck et al. 1977). Dyspnea was observed in goats and cows exposed to 5,000 and 7,700 mg/kg of Cellulube 220, respectively (Dollahite and Pierce 1969). Because the symptoms did not occur until 19 days after dosing, it is not likely to be the result of acetylcholinesterase inhibition; however, the cause of the dyspnea is not known. In rats acutely exposed to 5,000 mg/kg of Durad 110 or Durad 220B, chromorhinorrhea was observed. No respiratory effects were observed in rats exposed by gavage to ≤350 mg/kg of tributyl phosphate for 18 weeks (Laham et al. 1985).

Histological examination of the lungs, nose, and trachea revealed no treatment-related lesions in Fischer 344 rats and $B_6C_3F_1$ mice orally exposed to tricresyl phosphate (NTP 1994). Dosing regimens (highest doses in mg/kg/day in parenthesis) were as follows: 13-week feeding (rats 770, mice 1,050); 13-week gavage, 5 days a week (rats 800, mice 800); and 2-year feeding (rats 15, mice 37).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding respiratory effects in humans or animals after oral exposure to polyalphaolefin hydraulic fluids.

Cardiovascular Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding cardiovascular effects in humans or animals after oral exposure to mineral oil hydraulic fluids.

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Organophosphate Ester Hydraulic Fluids. No studies were located regarding cardiovascular effects in humans after oral exposure to organophosphate ester hydraulic fluids.

No gross or histological alterations in the cardiovascular system or changes in heart weight were observed in rabbits acutely exposed to ≤480 mg/kg/day of Cellulube 220 (Carpenter et al. 1959), in chickens acutely exposed to ≤720 mg/kg/day of Cellulube 220 (Carpenter et al. 1959), or in rats exposed to 50 mg/kg/day of Pydraul90E (Monsanto 1979) for an intermediate duration. Similar results were seen in rats exposed to 500 mg/kg of a fluid designated MIL-H-83306 (Mattie et al. 1993) for 26 days or to tributyl phosphate for 18 weeks (Laham et al. 1985). Histological examination of the heart revealed no treatment-related lesions in Fischer 344 rats and B6C3F, mice orally exposed to tricresyl phosphate (NTP 1994). Dosing regimens (highest doses in mg/kg/day in parenthesis) were as follows: 13-week feeding (rats 770, mice 1,050); 13-week gavage, 5 days a week (rats 800, mice 800); and 2-year feeding (rats 15, mice 37).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding cardiovascular effects in humans after oral exposure to polyalphaolefin hydraulic fluids.

No cardiovascular effects were observed in rats exposed by gavage to 1,000 mg/kg of a polyalphaolefin fluid designated MIL-H-83282 (Mattie et al. 1993).

Gastrointestinal Effects.

Mineral Oil Hydraulic Fluids. Subserosal hemorrhaging was observed in the small and large intestine and the omentum of a child who accidentally ingested a lethal amount of automobile transmission fluid (Perrot and Palmer 1992). Focal gastritis with edema and necrosis were observed in 2 of 4 rats exposed by gavage to 1,000 mg/kg MILH- 5606 for 26 days (Mattie et al. 1993).

Organophosphate Ester Hydraulic Fluids. In a case report and in the report of an outbreak of organophosphate ester poisoning, vomiting, diarrhea, and gastric upset were found (Goldstein et al. 1988; Srivastava et al. 1990). Gastrointestinal effects may well have a neurological component, because of known anti-cholinesterase properties of organophosphate esters. Cholinesterase inhibition in the gastrointestinal

tract is commonly manifested as diarrhea. See Section 2.2.2.4 for a more complete discussion of cholinesterase inhibition.

The most commonly reported gastrointestinal tract effect observed in animals orally exposed to organophosphate ester hydraulic fluids is diarrhea. Following acute exposure, diarrhea has been observed in rats exposed to 5,775 mg/kg of Durad MP280 (Gaworski et al. 1986) or 5,750 mg/kg Fyrquel 220 (Gaworski 500 mg/kg/day of Fyrquel 150 (Beck et al. 1977). Diarrhea was also observed in a cow exposed to 8,333 mg/kg/day of Cellulube 220 for an intermediate duration (Dollahite and Pierce 1969). Other gastrointestinal effects reported in cows acutely exposed include abdominal pain at 500 mg/kg/day of Fyrquel 150 (Beck et al. 1977) and tympanitis at 7,700 mg/kg/day of Cellulube 220 (Dollahite and Pierce 1969). Hypersalivation is reported for rats exposed to a 325 mg/kg/day dose of tri-n-butyl phosphate (Healy et al. 1995) over 13 weeks and may also be a neurological effect, not a true gastrointestinal effect. Histological examination of gastrointestinal tissues revealed no treatment-related lesions in Fischer 344 rats and B6C3F_1 mice orally exposed to tricresyl phosphate (NTP 1994). Dosing regimens (highest doses in mg/kg/day in parenthesis) were as follows: 13-week feeding (rats 770, mice 1,050); 13-week gavage, 5 days a week (rats 800, mice 800); and 2-year feeding (rats 15, mice 37).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding gastrointestinal effects in humans or animals after oral exposure to polyalphaolefm hydraulic fluids.

Hematological Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding hematological effects in humans after oral exposure to mineral oil hydraulic fluids.

A statistically significant reduction of 16% in the percentage of lymphocytes in whole blood was reported in rats receiving 1,000 mg/kg/day ME-H-5606 for 26 days (Mattie et al. 1993).

Organophosphate Ester Hydraulic Fluids. No studies were located regarding hematological effects in humans after oral exposure to organophosphate ester hydraulic fluids.

2. HEALTH EFFECTS

In rats exposed for intermediate durations at 250 mg/kg/day to tricresyl phosphate for 90 days, 250 mg/kg/day dibutyl phenyl phosphate for 91 days, or 250 mg/kg/day of trimethyl phosphate for 9 weeks, decreased hematocrit, erythrocyte counts and hemoglobin were reported (Healy et al. 1991; Oishi et al. 1982); at 500-1,000 mg/kg/day of MIL-H-83306, hemoglobin, mean cell hemoglobin, and mean cell hemoglobin concentration were reduced (Mattie et al. 1993). In other intermediate-duration studies, no effect on hematological parameters was observed in rats exposed to 50 mg/kg/day Pydraul 90 E (Monsanto 1979), ≤ 350 mg/kg/day of tributyl phosphate (Laham et al. 1985; Oishi et al. 1982), ≤800 mg/kg/day of tricresyl phosphate (Latendresse et al. 1994a, 1994b), or ≤250 mg/kg/day trioctyl phosphate (Oishi et al. 1982). Similar results were reported in rabbits exposed to ≤480 mg/kg/day Cellulube 220 (Carpenter et al. 1959). No alteration in hematological parameters was noted in Fischer 344 rats and $B_6C_3F_1$, mice orally exposed to tricresyl phosphate (NTP 1994). Dosing regimens (highest doses in mg/kg/day in parenthesis) were as follows: 13-week feeding (rats 770, mice 1,050); 13-week gavage, 5 days a week (rats 800, mice 800); and 2-year feeding (rats 15, mice 37).

Polyalphaolefm Hydraulic Fluids. No studies were located regarding hematological effects in humans after oral exposure to polyalphaolefin hydraulic fluids.

Reductions of approximately 10% in total hemoglobin and mean cell hemoglobin were observed in rats receiving 1,000 mg/kg/day of MIL-H-83282LT for 4 weeks (Mattie et al. 1993). A 47% increase in white blood cell counts was also observed in this study. No effects on hematological parameters were seen in rats similarly exposed to MIL-H-83282 (Mattie et al. 1993).

Musculoskeletal Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding musculoskeletal effects in humans or animals after oral exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding musculoskeletal effects in humans after oral exposure to organophosphate ester hydraulic fluids.

No gross or histological alterations were observed in skeletal muscle following acute exposure to Cellulube 220. The identified NOAEL values are 480 mg/kg/day in rabbits and 720 mg/kg/day in chickens (Carpenter et al. 1959). Muscle wasting was reported for cows exposed to a Fyrquel product containing tri-*ortho*-cresyl

phosphate (Julien et al. 1976). Histological examination of bone revealed no treatment-related lesions in Fischer 344 rats and $B_6C_3F_1$ mice orally exposed to tricresyl phosphate (NTP 1994). Dosing regimens (highest doses in mg/kg/day in parenthesis) were as follows: 13-week feeding (rats 770, mice 1,050); 13-week gavage, 5 days a week (rats 800, mice 800); and 2-year feeding (rats 15, mice 37).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding musculoskeletal effects in humans or animals after oral exposure to polyalphaolefin hydraulic fluids.

Hepatic Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding hepatic effects in humans after oral exposure to mineral oil hydraulic fluids.

A 32% increase in liver weights, along with a 187% increase in peroxisomal beta-oxidation activity, was noted in rats exposed to 1,000 mg/kg/day MIL-H-5606 for 26 days (Mattie et al. 1993). The toxicological significance of the changes in peroxisomal enzyme activities is unclear.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding hepatic effects in humans after oral exposure to organophosphate ester hydraulic fluids.

No gross or histological hepatic alterations were observed in rabbits exposed to ≤480 mg/kg/day or chickens exposed to up to 720 mg/kg/day, respectively, of Cellulube 220 for an acute duration (Carpenter et al. 1959). No hepatic effects were reported in rats exposed to 50 mg/kg/day of Pydraul 90E for an intermediate duration (Monsanto 1979). Several intermediate-exposure rat studies showed liver effects for organophosphate esters. Liver weight increases were shown for tributyl phosphate at 250 mg/kg/day (Laham et al. 1985; Oishi et al. 1982), trioctyl phosphate at 250 mg/kg/day (Oishi et al. 1982), 2-ethylhexyl diphenyl phosphate at 220 mg/kg/day (Noda et al. 1984), dibutyl phenyl phosphate at 250 mg/kg/day (Healy et al. 1991), butylated triphenyl phosphate at 1,000 mg/kg/day, tricresyl phosphate at 400 mg/kg/day (Latendresse et al. 1994b), and MIL-H-83306 at 500 mg/kg/day (Mattie et al. 1993). Blood urea nitrogen was also decreased in rats receiving 500 mg/kg/day MIL-H-83306 (Mattie et al. 1993). Histopathological evidence for hepatic effects after exposure to MIL-H-83306 (increased smooth endoplasmic reticulum) was found in rats exposed to 500 mg/kg/day for 26 days (Mattie et al. 1993). Changes in hepatic vacuolation and fatty accumulation were seen in rats exposed to 250 mg/kg/day dibutyl phenyl phosphate for 91 days (Healy et al. 1991).

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No histopathologic evidence of hepatic changes was seen in Fischer 344 rats orally exposed to tricresyl phosphate for 13 weeks in feed (≤770 mg/kg/day) or by gavage for 13 weeks, 5 days a week (≤800 mg/kg/day) (NTP 1994). Minimal papillary hyperplasia of the gall bladder mucosa was seen in male $B6C3F_1$ mice exposed to tricresyl phosphate in feed at 110 mg/kg/day for 13 weeks; this sign was characterized as mild in female mice similarly exposed at 230 mg/kg/day (NTP 1994). These signs were not seen in mice exposed for 13 weeks, 5 days a week by gavage at ≤800 mg/kg/day (NTP 1994). In a chronic duration study, male mice exposed to 13 mg/kg/day tricresyl phosphate for 105 weeks showed increased incidences of clear cell foci, fatty change and ceroid pigmentation (NTP 1994). This effect was not seen in female mice exposed to ≤37 mg/kg/day, or in rats exposed for 104 weeks at ≤15 mg/kg/day.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding hepatic effects in humans after oral exposure to polyalphaolefin hydraulic fluids.

Increased serum alkaline phosphatase was observed in rats receiving 1,000 mg/kg/day of MIL-H-83282 for 4 weeks but not in rats similarly exposed to 1,000 mg/kg/day MIL-H-83282LT (Mattie et al. 1993). Increased peroxisomal beta-oxidation rates were seen after exposure to both fluids, but the toxicological significance of this finding is unclear (Mattie et al. 1993).

Renal Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding renal effects in humans after oral exposure to mineral oil hydraulic fluids.

Persistent diuresis, proteinuria, and an increased urinary protein/creatinine ratio were observed in rats receiving 1,000 mg/kg/day MIL-H-5606 for 26 days (Mattie et al. 1993). Hyaline droplets in the proximal tubules were also noted at histopathological examination.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding renal effects in humans after oral exposure to organophosphate ester hydraulic fluids.

No gross or histological alterations were observed in rabbits exposed to ≤480 mg/kg/day of Cellulube 220 for an acute duration (Carpenter et al. 1959) or rats exposed to 50 mg/kg/day of Pydraul 90E for an intermediate duration (Monsanto 1979). Several reports of urinary bladder hyperplasia were found with

exposure levels to dibutyl phenyl phosphate at 50 mg/kg/day (Healy et al. 1991), to tributyl phosphate at 200 mg/kg/day (Laham et al. 1985) for intermediate-duration exposures. Urinary bladder hyperplasia was also reported in rats exposed to 32.5 mg/kg/day tributyl phosphate for 24 months (FMC 1994a). Kidney weights and blood urea nitrogen increased in rats at 250 mg/kg/day tributyl phosphate (Oishi et al. 1982) and diuresis, proteinuria, and an increase in urinary protein/creatinine ratio were observed in rats exposed to 500 mg/kg/day MIL-H-83306 for 26 days (Mattie et al. 1993). Signs of renal papillary edema and/or necrosis were observed in female rats exposed to 430 mg/kg/day tricresyl phosphate by feed for 13 weeks and in males at 750 mg/kg/day (NTP 1994). These signs were not observed when rats were exposed to ≤800 mg/kg/day for 13 weeks by gavage, 5 days a week (NTP 1994). Evidence for renal tubule regeneration was observed in male mice exposed to 900 mg/kg/day tricresyl phosphate in feed for 13 weeks, but not in female mice similarly exposed (NTP 1994). As in rats, no renal pathology was observed in mice exposed by gavage for 13 weeks, 5 days a week to ≤800 mg/kg/day.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding renal effects in humans after oral exposure to polyalphaolefin hydraulic fluids.

An increased urinary protein/creatinine ratio was observed in rats exposed to 1,000 mg/kg/day MIL-H-83282 for 4 weeks, and diuresis was seen in rats similarly exposed to MIL-H-83282LT (Mattie et al. 1993).

Endocrine Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding endocrine effects in humans or animals after oral exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding endocrine effects in humans after oral exposure to organophosphate ester hydraulic fluids.

Effects on the adrenal cortex have been observed in intermediate-duration studies for several organophosphate hydraulic fluids. Exposure of rats to 1,700 mg/kg/day of a butylated triphenyl phosphate fluid resulted in enlargement of the adrenals and lipidosis and cytoplasmic vacuolization of the adrenal cortex (Latendresse et al. 1994a). Similar results were observed in this study with exposure to tricresyl phosphate at 400 mg/kg/day. An important enzyme in steroid synthesis, neutral cholesteryl ester hydrolase, was significantly inhibited with both treatments. In a reproductive toxicity study (Chapin et al. 1988) in

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which male and female mice were exposed to 62.5 mg/kg of a mixture of tricresyl phosphates containing <0.1% pure TOCP, hypertrophy of the zona fasciculata cells and brown degeneration of cells in the juxtamedullary zone were observed in the adrenal gland. Cytoplasmic vacuolization of the adrenal cortex was also observed in rats exposed to tricresyl phosphate at all doses tested both in feed (55-770 mg/kg/day) and by gavage (50-800 mg/kg/day) for 13 weeks (NTP 1994). Similar results were observed in mice in 13-week feeding and gavage exposures in this study. In a 104-week exposure in rats, this sign was not seen in males at 13 mg/kg/day or females at 7 mg/kg/day, but was observed in 36 of 50 females exposed at 15 mg/kg/day.
Increased severity of ceroid pigmentation was observed in the adrenal cortex of mice exposed to 7-8 mg/kg/day tricresyl phosphate (the lowest dose tested for 105 weeks) (NTP 1994).

No histopathological changes in endocrine tissues (adrenal glands and thyroid) were noted in rabbits receiving ≤480 mg/kg/day Cellulube 220 for 114 days (Carpenter et al. 1959), or in rats receiving ≤350 mg/kg/day tributyl phosphate for 18 weeks (Laham et al. 1985).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding endocrine effects in humans or animals after oral exposure to polyalphaolefin hydraulic fluids.

Dermal Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding dermal effects in humans or animals after oral exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding dermal effects in humans after oral exposure to organophosphate ester hydraulic fluids.

Scabbing was observed in some rats exposed to Santicizer 154 at 300 mg/kg/day for 14 days (IRDC 1981).
No gross or histological alterations were observed in chickens exposed to 720 mg/kg/day of Cellulube 220 for an acute duration (Carpenter et al. 1959). Histological examination of the skin revealed no treatmentrelated lesions in Fischer 344 rats and B6C3Fi mice orally exposed to tricresyl phosphate (NTP 1994). Dosing regimens (highest doses in mg/kg/day in parenthesis) were as follows: 13-week feeding (rats 770, mice 1,050); 13-week gavage, 5 days a week (rats 800, mice 800); and 2-year feeding (rats 15, mice 37).

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Polyalphaolefin Hydraulic Fluids. No studies were located regarding dermal effects in humans or animals after oral exposure to polyalphaolefin hydraulic fluids.

Ocular Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding ocular effects in humans or animals after oral exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding ocular effects in humans after oral exposure to organophosphate ester hydraulic fluids.

No gross or histological alterations were observed in chickens exposed to 720 mg/kg/day of Cellulube 220 for an acute duration (Carpenter et al. 1959). No longer-term studies examining ocular end points were located.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding ocular effects in humans or animals after oral exposure to polyalphaolefin hydraulic fluids.

Body Weight Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding body weight effects in humans after oral exposure to mineral oil hydraulic fluids.

In acute lethality studies, no significant changes in growth were observed in rats administered 5,000 mg/kg of Sunsafe F, Quintolubric 9583OW, Houghto-Safe 5047F, or Pyroguard A-443 (Kinkead et al. 1989b, 19SS), or 4,500 mg/kg of a mineral oil meeting military specifications of MLH-5606 (Kinkead et al. 1985). No effect on body weight was observed in rats orally exposed to 1,000 mg/kg/day MIL-H-5606 for 26 days (Mattie et al. 1993).

Organophosphate Ester Hydraulic Fluids. No studies were located regarding body weight effects in humans after oral exposure to organophosphate ester hydraulic fluids.

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Weight loss has been observed in rats exposed to a single dose of 5,775 mg/kg of Durad MP280 (Gaworski et al. 1986) in chickens receiving 10,000 mg/kg/day of Reofos 65 and 15,000 mg/kg/day of Fyrquel EHC for acute durations (Mortensen and Ladefoged 1992), and in chickens receiving 1,333 mg/kg/day of Durad 110 for an intermediate duration (FMC 1986). No changes in body weight gain have been reported in rats and chickens exposed to a single dose of ≥5,000 mg/kg of a number of hydraulic fluids including cyclotriphosphazene (Kinkead et al. 1992c; MacEwen and Vemot 1985), Durad 550B (FMC 1992a), Durad 220B (FMC 1990a), Durad 110 (FMC 1990a), Durad 300 (FMC 1990a), and Fyrquel 220 (Gaworski et al. 1986; Kinkead et al. 1992a). Maternal rats showed a 35% reduced body weight gain in a 10-day exposure to 5,000 mg/kg/day of Santicizer 141 (Robinson et al. 1986). In a dose-finding study using 5 pregnant rats per group, a 12% decrease in maternal weight gain was noted at 200 mg/kg/day tributyl phosphate (Noda et al. 1994) but in a larger study with 20 animals per group, only minor body weight reductions were observed at 500 mg/kg/day. Several intermediate-duration studies showed reduction in body weight gain in rats or mice. Thirteen-week feeding exposures to tricresyl phosphate in rats at 430 mg/kg/day were associated with an 11% reduction in body weight in both males and females (NTP 1994). Exposure to 750 mg/kg/day caused a 33% decrease in body weight in males. Treatment by gavage for 13 weeks, 5 days a week did not affect female body weight at ≤800 mg/kg/day; male body weight was decreased 13% at this dose (NTP 1994). Body weight effects were also reported in mice in this study, decreases greater than 10% were seen in female mice at 530 mg/kg/day and above and in males at 900 mg/kg/day exposed to tricresyl phosphate by feed. Gavage doses greater than 400 mg/kg/day also caused decreased body weight (NTP 1994). Dibutyl phenyl phosphate exposure for 91 days at 250 mg/kg/day in female rats was observed to cause a 15% body weight reduction (Healy et al. 1991). Butylated triphenyl phosphate exposure at 1,000 mg/kg/day for 106 days caused an 11-17% decrease in body weight in Fischer 344 rats (Latendresse et al. I994b). Similar results have been reported with exposure to tributyl phosphate in rats: a 15% decrease at 300 mg/kg/day for 18 weeks (Laham et al. 1985) and an 11% decrease at 250 mg/kg/day for 9 weeks (Oishi et al. 1982). No changes in body weight gain were observed in rats exposed to 50 mg/kg/day of Pydraul 90E (Monsanto 1979) and chickens exposed to 270 mg/kg/day of Durad 110 (FMC 1986) for intermediate durations. Twoyear feeding exposure of rats and mice to tricresyl phosphate at 13-37 mg/kg/day produced no effect on body weight (NTP 1994).

Polyalphaolefzn Hydraulic Fluids. No studies were located regarding body weight effects in humans after oral exposure to polyalphaolefm hydraulic fluids.

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No changes in body weight gain were observed in rats receiving single doses of 4,250 mg/kg of polyalphaolefin hydraulic fluids designated as DTNSRDC N448, N501, N5 17, N5 18, N525, and N527 (MacEwen and Vemot 1983); MIL-H-83282 (Kinkead et al. 1985); 5,000 mg/kg of B85-174 (Kinkead et al. 1987b); or MIL-H-83282LT (Kinkead et al. 1992b). Similar results were reported in 4-week exposures to 1,000 mg/kg/day MIL-H-83282 and MIL-H-83282LT in rats (Mattie et al. 1993).

2.2.2.3 Immunological and Lymphoreticular Effects

Mineral Oil Hydraulic Fluids. No studies were located regarding immunological or lymphoreticular effects in humans or animals after oral exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding immunological or lymphoreticular effects in humans after oral exposure to organophosphate ester hydraulic fluids.

Rats exposed for 6 weeks to 2.5 mg/kg/day of tricresyl phosphate showed decreased serum antibody titers to tetanus and decreased immunoglobin levels (Banerjee et al. 1992). In a 16-day gavage study with tricresyl phosphate, serious effects on immunological/lymphoreticular tissues were observed (NTP 1994). Male and female rats that received 2900 mg/kg/day tricresyl phosphate had increased incidences of lymphoid depletion and necrosis of the spleen, thymus and the mandibular lymph node; the severity of these lesions ranged from mild to marked (NTP 1994). Significantly reduced thymus weight was observed at 1,450 mg/kg/day. Necrosis of the spleen, thymus, and mandibular lymph node and lymphoid depletion of the thymus were also observed in mice at 2,900 mg/kg/day (NTP 1994). The NOAEL value in this study was 1,452 mg/kg/day. At reduced doses in subsequent studies, histological examination of bone marrow, spleen, thymus and mandibular and mesenteric lymph nodes revealed no treatment-related lesions in Fischer 344 rats and $B_6C_3F_1$ mice orally exposed to tricresyl phosphate (NTP 1994). Dosing regimens (highest doses in mg/kg/day in parenthesis) were as follows: 13-week feeding (rats 770, mice 1,050); 13-week gavage, 5 days a week (rats 800, mice 800); and 2-year feeding (rats 15, mice 37).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding immunological or lymphoreticular effects in humans after oral exposure to polyalphaolefin hydraulic fluids.

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Histopathological analysis of the thymus, lymph nodes, and spleen of rats exposed to 1,000 mg/kg/day MIL-H-83282 or MIL-H-83282LT for 4 weeks revealed no treatment-related changes in these tissues (Mattie et al. 1993).

2.2.2.4 Neurological Effects

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Tables 2-4,2-5, and 2-6 and plotted in Figures 2-4,2-5, and 2-6 for mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, and polyalphaolefin hydraulic fluids, respectively.

Mineral Oil Hydraulic Fluids. No studies were located regarding neurological effects in humans after oral exposure to mineral oil hydraulic fluids.

Mineral oil hydraulic fluids sometimes contain organophosphate ester additives; however, no symptoms of acute cholinergic toxicity or delayed neuropathy were seen in several studies with animals treated with single oral doses of mineral oil hydraulic fluids. Single gavage doses of several hydraulic fluids at doses of ≈5,000 mg/kg produced no clinical signs of neurotoxicity within 14 days of dosing in Fischer 344 rats; tested fluids include several water-in-oil emulsion types of hydraulic fluids (Pyroguard A-443, Houghto-Safe 5047F, Quintolubric 9583OW, and Sunsafe F) (Kinkead et al. 1987a, 1988) and a U.S. military MIL-H-5606 fluid (Kinkead et al. 1985). Single gavage doses of a MIL-H-5606 hydraulic fluid (5 mL/kg or ≈4,500 mg/kg) produced no clinical signs of acute neurotoxicity or delayed neuropathy in Leghorn chickens within 2 1 days of dosing, nor did it produce histological changes in peripheral or central nervous system (tissues examined were not specified) like those produced in positive control chickens treated with 500 mg/kg tri-*ortho*-cresyl phosphate (Kinkead et al. 1985).

No studies were located regarding neurological effects in animals after intermediate or chronic-duration oral exposures to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. A brief overview of organophosphate ester neurotoxicity is presented in Section 2.2.1.4.

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A number of human poisonings have been reported, dating back to the 1930s in which the primary effects of tricresyl phosphates were neurological (Goldstein et al. 1988; Senanayake and Jeyaratnam 1981; Srivastava et al. 1990). Though doses are difficult to ascertain, estimated exposure to 50-100 mg/kg/day resulted in facial weakness, severe dysarthria (difficulty of speech due to muscular control problems stemming from central or peripheral nerve damage), loss of reflexes and myoclonic jerking in a 4-year-old boy (Goldstein et al. 1988) and polyneuropathy in young Sri Lankan girls (Senanayake and Jeyaratnam 1981) exposed to 5-10 mg/kg/day for 14 days. The boy fully recovered in 5 weeks. One year after ingesting 5-7 doses of tricresyl phosphate, the young women still reported reduced muscular strength. Abou-Donia and Lapadula (1990) have estimated that there have been more than 40,000 cases of OPIDN. More than 20,000 cases occurred in the United States in the 1930s as a result of people consuming a contaminated extract of ginger called “Jamaican Ginger.” Subsequent analysis revealed that these cases of delayed neuropathy were caused by the presence of a specific isomer of tricresyl phosphate, tri-*ortho*-cresyl phosphate (TOCP), in the extract.

Many of the studies on the neurological effects of oral exposure to organophosphate ester hydraulic fluids in animals have employed chickens as models instead of the more commonly used rodent models. For reasons that are not well understood, organophosphate-induced delayed neuropathy can be induced in chickens and cats, but not in mice or rats (Abou-Donia and Lapadula 1990).

Several organophosphate ester hydraulic fluids produced neurological effects, including acute cholinergic toxicity and signs of organophosphate-induced delayed neuropathy (OPIDN), in chickens after acute gavage administration (see Table 2-5). Fyrquel EHC produced incoordination, inability to stand and eventually ataxia in chickens after a single dose of 11,350 mg/kg (Stauffer Chemical Co. 1980); spinal cord lesions with minor signs of neuropathy at 5,000 mg/kg and ataxia at 10,000 mg/kg (Mortensen and Ladefoged 1992); and decreased activities of brain neurotoxic esterase and plasma cholinesterase without signs of neurotoxicity at 1,140 mg/kg (Stauffer Chemical Co. 1981). Brain neurotoxic esterase activity was reduced 94% by a single dose of 11,350 mg/kg Fyrquel EHC, a dose which produced ataxia (Stauffer Chemical Co. 1980). Chickens dosed with either tributyl phosphate or dibutyl phenyl phosphate exhibited apparent cholinergic signs (salivation, diarrhea, impaired respiration) for 2-4 days after single doses near the LD_{50} for these compounds but did not show significant reduction in brain acetylcholinesterase or further signs of neurotoxicity (Canington et al. 1989). Tributoxyethyl phosphate significantly inhibited brain acetylcholinesterase (45%), but neither acute cholinergic signs nor further signs of neurotoxicity developed. Inhibition of NTE and motor incoordination were observed in chickens receiving a single oral dose of 11,700 mg/kg isopropyl triphenyl phosphate (Sprague et al. 1984), but OPIDN did not develop. Reofos 65 produced minor

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histological changes in peripheral nerves without cholinergic symptoms or signs of delayed neuropathy at doses ≤5,000 mg/kg (Mortensen and Ladefoged 1992).

Tricresyl phosphate caused ataxia, axonal degeneration and reduction of NTE at 60 mg/kg/day over 10 weeks in chickens (Freudenthal et al. 1993). Skydrol LD-4 and Skydrol 500B-4 produced decreased activities of brain neurotoxic esterase (-46%), brain acetylcholinesterase (-18%), and plasma butyrylcholinesterase (-78%), as well as cholinergic symptoms at respective LD_{50} levels of 2,594 and 2,559 mg/kg in chickens. No clear signs of delayed neuropathy developed in survivors at doses as high as 5,000 mg/kg (Monsanto 1987c, 1987d). U.S. military fluids designated as Durad MP280 and Cellulube 220 produced distinct clinical signs of OPIDN (ataxia and paralysis) in chickens after 5 days of dosing with 240 and 60 mg/kg/day, respectively (Carpenter et al. 1959; Gaworski et al. 1986). A tricresyl phosphate fluid designated TCP-1 caused leg and wing weakness and paralysis in chickens receiving 240 mg/kg/day for 5 days (Friess et al. 1959). Fyrquel 220 and Fyrquel 150 each produced distinct clinical signs of OPIDN in chickens after 5-day administrations of respective doses of 5,000 mg/kg/day (FMC 1977a) and 240 mg/kg/day (Stauffer Chemical Co. 1971). Fyrquel 220 at a dose of 420 mg/kg/day had no effect (FMC 1977a). Fourteen days of tricresyl phosphate exposure in mice caused cholinergic signs such as piloerection, tremors, and lethargy at 2,275 mg/kg/day, but not OPIDN (Chapin et al. 1988)

Another group of organophosphate ester hydraulic fluids produced no signs of neurotoxicity in chickens following acute gavage administration. Fluids that produced no neurotoxic signs in chickens (with the maximum dose level at which they were tested in parenthesis) included U.S. military fluids MIL-H-19457B and MIL-H-19457(3 (420 mg/kg/day for 5 days [Gaworski et al. 1986; Kinkead et al. 1989b]), Pydraul 50E (20,000 mg/kg/day for 3 days [Monsanto 19791 and 5,000 mg/kg/day for 4 or 5 days [Ciba-Geigy 1973; FMC 1977b]), Pydraul 29ELT (20,000 mg/kg/day for 3 days [Monsanto 1979]), and Pydraul 90E (20,000 mg/kg/day for 3 days [Monsanto 19791). Each of these studies provided sufficient periods (>18 days) to observe signs of delayed neuropathy.

Administration of organophosphate ester hydraulic fluids has produced neurological effects in-species other than chickens. Cellulube 220 produced delayed hindlimb paralysis in two goats 19-36 days after single doses of 5,000 or 10,000 mg/kg, and incoordination, accompanied with demyelination and axonal swelling in peripheral nerves, and increased cellularity in dorsal and ventral spinal nerve roots in a calf 19 days after a single dose of 7,700 mg/kg (Dollahite and Pierce 1969). Beck et al. (1977) observed acute signs of cholinesterase inhibition (diarrhea, rapid respiration, salivation, miosis) that eventually led to death in calves

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given 500, 1,000, or 2,000 mg/kg/day Fyrquel 150 by gavage for 10 days. The dose level did not influence the onset or severity of clinical signs. Delayed hindlimb paralysis developed in two cows given single gavage doses of 500 or 1,000 mg/kg Fyrquel 150; histological examination of the spinal cord revealed axonal degeneration and demyelination (Beck et al. 1977). The onset of hindlimb paralysis was observed after the cessation of cholinesterase effects on either day 15 or 19.

No clinical signs of neurotoxicity were observed in rats after acute gavage administration in lethality studies of several organophosphate ester hydraulic fluids tested at dose levels as high as 5,000 mg/kg. Tested materials included Durad 300 (FMC 1990a), Durad 110 (FMC 1990a), Durad 220B (FMC 1990a), Durad 550B (FMC 1992a), and a cyclotriphosphazene based fluid (Kinkead et al. 1992c; MacEwen and Vemot 1985). Durad 125 produced an 85% inhibition of serum cholinesterase in rats, without producing cholinergic signs (tremors, diarrhea) like those produced in positive controls treated with tri-*ortho*-cresyl phosphate (FMC 199 la). Cellulube 220, a fluid that produced definite signs of delayed neuropathy in goats and cows, produced no signs of neurotoxicity in rats treated with 20,000 mg/kg (Dollahite and Pierce 1969).

No studies were located regarding neurological effects in animals after chronic oral exposure to organophosphate ester hydraulic fluids, but three hydraulic fluids have been tested for neurological effects in animals after intermediate dose administration. In a 90-day dietary study, administration of 50 mg/kg/day Pydraul90E to albino rats produced no effects on brain, plasma, or red blood cell cholinesterase activities, compared with controls, and no histological effects. The report did not mention the extent of the histological examination nor the occurrence of clinical signs of neurotoxicity (Monsanto 1979). In a 28day study with domestic chickens gavaged daily with Durad 110, an increased incidence of chickens with clinical signs of ataxia was observed at 1,333 mg/kg/day, but not at 444 mg/kg/day (FMC 1986). In a 90-day gavage study with Durad 110, chickens treated with 90 mg/kg/day displayed an increased incidence of ataxia and axonal damage in the spinal cord and peripheral nerves. The NOAEL for neurological effects was 20 mg/kg/day (FMC 1986). Cellulube 220 administered at a dose level of ≈8,333 mg/kg/day three times over a 56-day period produced incoordination in a calf after the last dose administration; axonal swelling in the peripheral nervous system was observed (Dollahite and Pierce 1969).

Neurological effects have also been observed with several organophosphate esters used currently or formerly in hydraulic fluids. Dibutyl phenyl phosphate decreased erythrocyte and brain acetylcholinesterase levels in female rats exposed by feed for 91 days at 250 mg/kg/day but not at 50 mg/kg/day (Healy et al. 1991). Male rats similarly exposed were unaffected. In Fischer 344 rats receiving tricresyl phosphate by gavage for

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16 days, decreased activity and grip strength were noted in females at 1,450 mg/kg/day and in males at 2,900 mg/kg/day (NTP 1994); no-effect levels were 730 mg/kg/day in females and 1,450 mg/kg/day in males. Thirteen-week exposures by gavage or feed in this strain of rats at ≤800 mg/kg/day tricresyl phosphate had no effect on neurological parameters or histology of brain, spinal cord or sciatic nerve (NTP 1994). In a 2-year feeding study with tricresyl phosphate in rats (0, 3, 6, or 13 mg/kg/day in males; 0,4,7, or 15 mg/kg/day in females), no histological evidence of treatment-related damage to nervous system tissues (brain, spinal cord, and sciatic nerve) was observed (NTP 1994).

Tricresyl phosphate exposure by feed for 13 weeks resulted in tremors in male B6C3F, mice receiving 900 mg/kg/day and decreased forelimb grip strength at 380 mg/kg/day (NTP 1994). Female mice exposed at 530 mg/kg/day also showed decreased hindlimb strength along with histopathological evidence of axonal degeneration in the spinal cord and sciatic nerve. NOAELs in this study were 180 mg/kg/day in males and 230 mg/kg/day in females. Tricresyl phosphate was more potent for inducing neurological effects when given by gavage. A 13-week exposure by gavage (5 days a week) produced multifocal degeneration of the spinal cord and sciatic nerve at 100 mg/kg/day (NTP 1994). No histologic evidence of treatment-related damage to brain, spinal cord, or sciatic nerve was seen in mice after a 2-year feed exposure to ≤37 mg/kg/day tricresyl phosphate (NTP 1994).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding neurological effects in humans after oral exposure to polyalphaolefin hydraulic fluids.

In a series of acute lethality studies on U.S. military fluids, single gavage doses (4,250 or 5,000 mg/kg) of one of several polyalphaolefin hydraulic fluids did not produce signs of neurological toxicity in rats within 14 days of dosing. Tested materials included fluids designated as DTNSRDC Nos. N448, N501, N517, N518, N525, and N527 (MacEwen and Vemot 1983); B85-174 (Kinkead et al. 1987b); MIL-H-83282LT (Kinkead et al. 1992b); MIL-H-83282 (Kinkead et al. 1985). Single gavage doses of MIL-H-83282 (7.5 mL/kg or 6,375 mg/kg) or MIL-H-83282LT (5,000 mg/kg) did not produce delayed neuropathy in Leghorn chicken hens within 21 days of dosing (Kinkead et al. 1985, 1992b). No other information was located on neurological effects in animals after oral exposure to polyalphaolefin hydraulic fluids.

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2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after oral exposure to mineral oil hydraulic fluids or to polyalphaolefin hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding reproductive effects in humans after oral exposure to organophosphate ester hydraulic fluids.

Data suggestive of adverse reproductive effects after an assumed acute oral exposure to organophosphate ester hydraulic fluids are restricted to an observation of reduced lactation and delayed estrus with no coincident gross lesions in cows that ingested grass contaminated with Fyrquel 150 (Beck et al. 1977).

There are a number of studies of intermediate duration which note reproductive effects in experimental animals. Rats exposed to 400 mg/kg/day tricresyl phosphate and 1,900 mg/kg/day butylated triphenyl phosphate for 40 days by gavage showed hypertrophy and vacuolization of ovarian interstitial cells (Latendresse et al. 1993). These results are supported by a study in which rats exposed by gavage for 20,40, and 60 days showed lipidosis in ovarian interstitial cells at 400 mg/kg/day tricresyl phosphate and 1,700 mg/kg/day butylated triphenyl phosphate, as well as testicular degeneration and decreased testicular weight at 400 mg/kg/day tricresyl phosphate (Latendresse et al. 1994a). An increase in abnormal sperm morphology and necrosis of seminiferous tubules were noted in male rats exposed to 100 mg/kg/day tricresyl phosphate by gavage, while decreased fertility and vacuolar cytoplasmic alteration of ovarian interstitial cells were noted in female rats exposed at 200 mg/kg/day to this compound for 66 days (Carlton et al. 1987). Latendresse et al. (1994b) reported decreased numbers of litters in rats exposed by gavage to 600, 1,000, and 1,700 mg/kg/day butylated triphenyl phosphate and 400 mg/kg/day tricresyl phosphate for 98 days. In the same study, 100% infertility, decreased testicular and epididymal weights, and increased ovarian weights were seen at 400 mg/kg/day tricresyl phosphate; and abnormal estrous cycles and decreased uterine weights were noted in female rats exposed to 1,000 mg/kg/day butylated triphenyl phosphate, all for 106 days. Decreased mating and fertility indices and decreased number of live pups per litter were seen after 105 days of exposure to 124 mg/kg/day in the feed (Chapin et al. 1988) but not at 62.5 mg/kg/day.

Reproductive changes in rats and mice were found in intermediate- and chronic-duration oral studies performed with tricresyl phosphate by the National Toxicology Program (NTP 1994). Ovarian interstitial cell hypertrophy was a common finding in both species and occurred at the lowest doses tested in rats in a

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13-week feeding study in rats (65 mg/kg/day) and a 13-week gavage study (50 mg/kg/day). In mice, this sign was observed at 50 mg/kg/day in a 13-week gavage study. These effects were seen at all doses tested, but did not increase in severity with dose. Interstitial cell cytoplasmic vacuolization was observed at 530 mg/kg/day in a 13-week feeding study, but hypertrophy was not. Seminiferous tubule atrophy was observed in rats at 430 mg/kg/day in 13-week feeding studies and at 400 mg/kg/day in 13-week gavage studies. Similar results were seen in mice treated by gavage, but not in mice exposed to tricresyl phosphate by feeding (NTP 1994).

In contrast, several studies did not report reproductive effects. Laham et al. (1985) reported no significant changes in the testes or ovaries in rats exposed by gavage to a high dose of 350 mg/kg/day tri-*n*-butyl phosphate for 18 weeks. No gross or histological alterations in the reproductive tract after acute oral exposure were observed in male rabbits gavaged with 480 mg/kg Cellulube 220 (Carpenter et al. 1959) or in chickens given ≤420 mg/kg of MIL-H-19457B or MIL-H-19457C (Kinkead et al. 1989b). No changes in gonad weight or histology were observed in male or female rats after oral exposure to Pydraul90E at a dietary concentration of 50 mg/kg/day for 90 days (Monsanto 1979).

In a 2-year feeding study in rats, ovarian interstitial cell hyperplasia was observed in rats exposed to 15 mg/kg/day tricresyl phosphate, but no effect was seen at 7 mg/kg/day (NTP 1994). No effects on male reproductive tissues were seen at ≤13 mg/kg/day. No effects on reproductive tissues in either sex were observed in 2-year feeding studies in mice (27 mg/kg/day in males, 37 mg/kg/day in females).

A neurotoxic isomer of tricresyl phosphate (tri-*ortho*-cresyl phosphate) altered testicular morphology and function as well as reproductive function after oral exposure in rats (Somkuti et al. 1987a, 1987b) (see Section 2.5).

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after oral exposure to mineral oil hydraulic fluids or to polyalphaolefin hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding developmental effects in humans after oral exposure to organophosphate ester hydraulic fluids.

2. HEALTH EFFECTS

Data suggestive of adverse developmental effects after an assumed acute oral exposure to organophosphate ester hydraulic fluids are restricted to an observation of retarded growth in calves of cows with reduced lactation, and "abnormal" growth in a calf of a cow that showed moderate ataxia, after the cows ingested grass probably contaminated with Fyrquel 150 (Beck et al. 1977).

None of the calves of 10 cows showed clinical signs of neurotoxicity after the cows were orally exposed to an unknown quantity of a Fyrquel hydraulic fluid reclamation waste that according to the authors possibly contained tri-*ortho*-cresyl phosphate (TOCP), and that was applied liberally to their backs one time as a treatment for ringworm (Julian et al. 1976). The cows were seen licking their backs and the backs of other cows; thus, the cows were orally and dermally exposed to organophosphate ester hydraulic fluids.

With acute-duration exposure to tricresyl phosphate and dibutyl phenyl phosphate, decreased litter size and pup survivability were found at 400 mg/kg/day (Carleton et al. 1987) and 50 mg/kg/day (Healy et al. 1991), respectively. Exposure to Santicizer 154 caused no developmental changes in the offspring of rats treated with ≤2,000 mg/kg/day for 14 days (Robinson et al. 1986). An 8% decrease in pup weight was reported in the offspring of rats treated during gestation with 1,000 mg/kg/day Phosflex 5 1 B, although the authors considered this effect to be secondary to maternal toxicity (Stauffer 1982). Increased incidence of rudimentary lumbar ribs were noted in offspring of rat dams treated with tributyl phosphate at 500 mg/kg/day over gestation days 7-17 (Noda et al. 1986). Dibutyl phenyl phosphate, a component of some organophosphate ester hydraulic fluids, decreased the postnatal survival of rat pups. Decreased survival to day 4 was observed in the F_{1a} pups (first litter) of rats exposed to 50 or 250 mg/kg/day and F_{1b} pups (second litter) of rats exposed to 5 or 50 mg/kg/day (but not to 250 mg/kg/day). The number of live offspring at weaning was also diminished in the F_{1a} pups in 50 and 250 mg/kg/day groups and F_2, pups of the 250 mg/kg/day group. In an attempt to determine if the reduced survival was due to *in utero* effects, the F_{1b} pups of the 250 mg/kg/day pups were cross-fostered with control pups. Reduced survival at day 4 and weaning was observed in the control pups raised by the high-dose rats. Decreased body weight gains were observed in the F, dams (parental) exposed to 250 mg/kg/day and F_1, dams exposed to 50 and 250 mg/kg/day. Effects on control pups, potentially exposed via treated dams are equivocal. Although surviva1 was reduced, the cause is not clear (Healy et al. 1991). Additionally, no changes were seen in the type or incidence of developmental anomalies observed in the pups of male and female rats that had been orally exposed to triphenyl phosphate, another component of some organophosphate ester hydraulic fluids at doses $\underline{<}$ 690 mg/kg/day for 91 days, including through mating and gestation (Welsh et al. 1987).

2. HEALTH EFFECTS

No intermediate- or chronic-duration oral studies examining developmental effects in animals were located.

2.2.2.7 Genotoxic Effects

Mineral Oil Hydraulic Fluids. No studies were located regarding genotoxic effects in humans or animals after oral exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding genotoxic effects in humans after oral exposure to organophosphate ester hydraulic fluids.

The incidence of nuclear anomalies in bone marrow interphase cells significantly increased ($p<0.05$) in Chinese hamsters gavaged on 2 consecutive days with 2,500 and 5,000 mg/kg/day of Reofos 50 (Ciba-Geigy 1984a), but not in those dosed with 1,250 mg/kg/day. The types of anomalies used in scoring were single "Howell-Jolly" bodies, fragments of nuclei in erythrocytes, micronuclei in erythroblasts, micronuclei in leucopoietic cells, and polyploidal cells.

Administration of single doses of ≤5,000 mg/kg Reofos 50 in sodium-carboxymethyl cellulose or Reolube HYD46 in arachid oil by gavage oil to four male and four female Chinese hamsters did not induce significant increases in sister chromatid exchanges in bone marrow cells (Ciba-Geigy 1983b, 1984b). Other genotoxicity studies for organophosphate ester hydraulic fluids are discussed in Section 2.5.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding genotoxic effects in humans or animals after oral exposure to polyalphaolefin hydraulic fluids.

2.2.2.8 Cancer

Mineral Oil Hydraulic Fluids. No studies were located regarding cancer in humans or animals after oral exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding cancer in humans after oral exposure to organophosphate ester hydraulic fluids.

2. HEALTH EFFECTS

A 2-year carcinogenicity bioassay of tricresyl phosphate in mice and rats showed no evidence of carcinogenicity in these species (NTP 1994). Doses (consumed in feed) were 137 mg/kg/day in mice and ≤15 mg/kg/day in rats. Dietary administration of tributyl phosphate was associated with transitional and squamous cell carcinomas of the bladder in rats after 2 years of exposure at 143.3 mg/kg/day (FMC 1994a). An increased incidence of hepatocellular adenomas in the liver was observed in mice after dietary administration of 455 mg/kg/day tributyl phosphate for 18 months (FMC 1994b).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding cancer in humans or animals after oral exposure to polyalphaolefin hydraulic fluids.

2.2.3 Dermal Exposure

The NOAEL and LOAEL values for each effect after dermal exposure are shown in Tables 2-7,2-8, and 2-9 for mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, and polyalphaolefin hydraulic fluids, respectively.

2.2.3.1 Death

Mineral Oil Hydraulic Fluids. No studies were located regarding death in humans after dermal exposure to mineral oil hydraulic fluids.

Several water-in-oil emulsion hydraulic fluids (Houghto-Safe 5047F, Sunsafe F, Pyroguard A-443, and Quintolubric 95830W) produced no deaths or signs of toxicity in rabbits within 14 days of single 24-hour exposures to occluded doses of 2,000 mg/kg spread evenly onto the backs and sides of the animals (Kinkead et al. 1987a, 1988). A U.S. military fluid designated as MIL-H-5606 likewise produced no deaths in rabbits within 14 days of 24-hour exposures to occluded doses of 1,800 mg/kg spread evenly onto the backs and sides of the animals (Kinkead et al. 1985). Additional information on lethality of mineral oil hydraulic fluids in animals after oral exposure was not located. -.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding death in humans after dermal exposure to organophosphate ester hydraulic fluids.

Table 2-7. Levels of Significant Exposure to Mineral Oil Hydraulic Fluids - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL		Reference Fluid Identity
				Less Serious	Serious	
ACUTE EXPOSURE						
Systemic						
Rabbit (New Zealand)	24 hr	Bd Wt	2000 mg/kg			Kinkead et al. 1987a; Kinkead et al. 1988 Houghto-Safe 5047F
Rabbit (New Zealand)	once	Dermal	0.1 mL			Kinkead et al. 1987a; Kinkead et al. 1988 Houghto-Safe 5047F
Rabbit (New Zealand)	once	Ocular		0.1 mL	(mild eye irritation)	Kinkead et al. 1987a; Kinkead et al. 1988 Houghto-Safe 5047F
Rabbit (New Zealand)	24 hr	Bd Wt	1800 mg/kg			Kinkead et al. 1985 MIL-H-5606
Rabbit (New Zealand)	once	Ocular	0.1 mL			Kinkead et al. 1985 MIL-H-5606
Rabbit (New Zealand)	24 hr	Dermal		0.5 mL	(moderate skin irritation; erythema and edema)	Kinkead et al. 1985 MIL-H-5606
Rabbit (New Zealand)	once	Dermal	0.1 mL			Kinkead et al. 1987a; Kinkead et al. 1988 Pyroguard A-443

Table 2-7. Levels of Significant Exposure to Mineral Oil Hydraulic Fluids - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL			Reference Fluid Identity
				Less Serious		Serious	
Rabbit (New Zealand)	24 hr	Bd Wt	2000 mg/kg				Kinkead et al. 1987a; Kinkead et al. 1988 Pyroguard A-443
Rabbit (New Zealand)	once	Ocular		0.1	(mild eye irritation)		Kinkead et al. 1987a; Kinkead et al. 1988 Pyroguard A-443
Rabbit (New Zealand)	once	Dermal	0.1 mL				Kinkead et al. 1987a; Kinkead et al. 1988 Quintolubric 95830W
Rabbit (New Zealand)	24 hr	Bd Wt	2000 mg/kg				Kinkead et al. 1987a; Kinkead et al. 1988 Quintolubric 95830W
Rabbit (New Zealand)	once	Ocular		0.1 mL	(mild eye irritation)		Kinkead et al. 1987a; Kinkead et al. 1988 Quintolubric 95830W
Rabbit (New Zealand)	once	Ocular		0.1 mL	(mild eye irritation)		Kinkead et al. 1987a; Kinkead et al. 1988 Sunsafe F
Rabbit (New Zealand)	24 hr	Bd Wt	2000 mg/kg				Kinkead et al. 1987a; Kinkead et al. 1988 Sunsafe F

Table 2-7. Levels of Significant Exposure to Mineral Oil Hydraulic Fluids - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL		Reference Fluid Identity
				Less Serious	Serious	
Rabbit (New Zealand)	once	Dermal	0.1 mL			Kinkead et al. 1987a; Kinkead et al. 1988 Sunsafe F
Immunological/Lymphoreticular						
Gn Pig (Hartley)	9 d 4x		61 mg/ cm^2/d			Kinkead et al. 1987a; Kinkead et al. 1988 Houghto-Safe 5047F
Gn Pig (Hartley)	9 d 4 x		0.01 g			Kinkead et al. 1985 MIL-H-5606
Gn Pig (Hartley)	9 d 4x		61 mg/ cm^2/d			Kinkead et al. 1987a; Kinkead et al. 1988 Pyroguard A-443
Gn Pig (Hartley)	9 d 4x			64 mg/cm^2 /d	(skin sensitization in 1/10 guinea pigs)	Kinkead et al. 1987a; Kinkead et al. 1988 Quintolubric 95830W
Gn Pig (Hartley)	9 d 4x		61 mg/ cm^2/d			Kinkead et al. 1987a; Kinkead et al. 1988 Sunsafe F

Bd Wt = body weight; d = day(s); Gn pig = guinea pig; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; x = time(s)

Table 2-8. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL		Reference Fluid Identity
				Less Serious	Serious	
ACUTE EXPOSURE						
Death						
Rabbit (New Zealand)	24 hr				>5000 mg/kg (LD_{50})	Johannsen et al. 1977 symmetrical triaryls
Rabbit (New Zealand)	24 hr				>3100 mg/kg (LD_{50})	Johannsen et al. 1977 TBP
Systemic						
Rat (Sprague-Dawley)	24 hr	Dermal	2000 mg/kg			FMC 1990c Durad 110
		Bd Wt	2000 mg/kg			
Rat (Sprague-Dawley)	24 hr	Dermal	2000 mg/kg			FMC 1990h Durad 220B
		Bd Wt	2000 mg/kg			
Rat (Sprague-Dawley)	24 hr	Dermal	2000 mg/kg			FMC 1990e Durad 300
		Bd Wt	2000 mg/kg			
Rabbit (New Zealand)	once	Ocular	0.1 mL			Kinkead et al. 1992c; MacEwen and Vernot 1985 cyclotriphos-phazene

Table 2-8. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL			Reference Fluid Identity
				Less Serious		Serious	
Rabbit (New Zealand)	24 hr	Dermal	2890 M mg/kg				Kinkead et al. 1992c; MacEwen and Vernot 1985 cyclotriphos-phazene
		Bd Wt	2890 M mg/kg				
Rabbit (New Zealand)	4 hr	Dermal	0.5 mL				FMC 1991b Durad 125
Rabbit (New Zealand)	4 hr	Dermal		0.5 mL	(mild erythema and skin thickening)		FMC 1992g Durad 550B
Rabbit (New Zealand)	once	Ocular	0.1 mL F				Gaworski et al. 1986; Kinkead et al. 1992d Durad MP280
Rabbit (New Zealand)	once	Dermal	0.5 mL F				Gaworski et al. 1986; Kinkead et al. 1992d Durad MP280
Rabbit (New Zealand)	once	Dermal	2300 mg/kg				Gaworski et al. 1986; Kinkead et al. 1992a Fyrquel 220
		Bd Wt		2300 mg/kg	(transient weight loss)		

Table 2-8. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL		Reference Fluid Identity
				Less Serious	Serious	
Rabbit (New Zealand)	once	Ocular	0.1 mL F			Gaworski et al. 1986; Kinkead et al. 1992e Fyrquel 220
Rabbit (New Zealand)	once	Dermal	0.5 mL F			Gaworski et al. 1986; Kinkead et al. 1992e Fyrquel 220
Rabbit (New Zealand)	once	Dermal	2 mL/kg			Gaworski et al. 1986 MIL-H-19457B
		Bd Wt		2 mL/kg	(transient weight loss)	
Immunological/Lymphoreticular						
Gn pig (Hartley)	10 d 4 x		0.1 mL M			Kinkead et al. 1992c; MacEwen and Vernot 1985 cyclotriphos-phazene
Neurological						
Rat (Sprague-Dawley)	24 hr		2000 mg/kg			FMC 1990c Durad 110
Rat (Sprague-Dawley)	24 hr		2000 mg/kg			FMC 1990e Durad 300

Table 2-8. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL		Reference Fluid Identity
				Less Serious	Serious	
Rabbit (New Zealand)	24 hr		2890 M mg/kg			Kinkead et al. 1992c; MacEwen and Vernot 1985 cyclotriphos-phazene
Chicken (NS)	2 x		5000 F mg/kg			Carrington et al. 1989 TBEP
INTERMEDIATE EXPOSURE						
Systemic						
Human	5 wk 3 x/wk	Dermal		0.2 mL	(14/53 erythema after at least 3 applications)	Monsanto 1980 Skydrol 500 B-4
Rabbit (New Zealand)	21 d 5 d/wk 6 hr/d	Resp	1000 mg/kg			Kinkead et al. 1990; Kinkead et al. 1989c cyclotriphos-phazene
		Cardio	1000 mg/kg			
		Gastro	1000 mg/kg			
		Hemato	1000 mg/kg			
		Musc/skel	1000 mg/kg			
		Hepatic	1000 mg/kg			
		Renal	1000 mg/kg			
		Endocr	1000 mg/kg			
		Ocular	1000 mg/kg			

Table 2-8. Levels of Significant Exposure to Organophosphate Ester Hydraulic Fluids - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL		Reference Fluid Identity
				Less Serious	Serious	
Rabbit (New Zealand)	21 d 5 d/wk 6 hr/d	Cardio	5750 mg/kg			MacEwen and Vernot 1983 Fyrquel 220
		Gastro	2875 mg/kg	5750 mg/kg	(soft feces)	
		Hemato	5750 mg/kg			
		Hepatic	5750 mg/kg			
		Renal	575 mg/kg	2875 mg/kg	(increased BUN and creatinine)	
		Dermal	5750 mg/kg			
Immunological/Lymphoreticular						
Human	5 wk 3 x/wk		0. 2 mL			Monsanto 1980 Skydrol 500 B-4
Rabbit (New Zealand)	21 d 5 d/wk 6 hr/d		1000 mg/kg			Kinkead et al. 1990; Kinkead et al. 1989c Cyclotri-phosphazene
Reproductive						
Rabbit (New Zealand)	21 d 5 d/wk 6 hr/d		1000 mg/kg			Kinkead et al. 1990; Kinkead et al. 1989c cyclotriphos-phazene

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; Musk/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; TBP = tributyl phosphate; wk = week(s); x = times

Table 2-9. Levels of Significant Exposure to Polyalphaolefin Hydraulic Fluids - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/	System	NOAEL	LOAEL		Reference Fluid Identity
				Less Serious	Serious	
ACUTE EXPOSURE						
Systemic						
Rat (Fischer- 344)	4 hr	Ocular		1120 mg/m^3	(eye irritation during exposure)	Kinkead et al. 1992b (MIL-H-83282LT)
Rabbit (albino)	4 hr	Dermal	142 mg/ cm^2			Kinkead et al. 1987b (B85-174)
Rabbit (New Zealand)	once	Bd Wt	2000 mg/kg			Kinkead et al. 1987b (B85-174)
Rabbit (New Zealand)	once	Ocular	0.1 mL			Kinkead et al. 1987b (B85-174)
Rabbit (New Zealand)	once	Ocular	0.1 mL			MacEwen and Vernot 1983 (DTNSRDC N517)
Rabbit (New Zealand)	24 hr	Bd Wt	1700 mg/kg			MacEwen and Vernot 1983 (DTNSRDC N517)
Rabbit (New Zealand)	24 hr	Dermal		0.5 mL	(mild skin irritant)	MacEwen and Vernot 1983 (DTNSRDC N517)
Rabbit (New Zealand)	24 hr	Dermal	0.5 mL			MacEwen and Vernot 1983 (DTNSRDC N518)
Rabbit (New Zealand)	once	Ocular	0.1 mL			MacEwen and Vernot 1983 (DTNSRDC N518)

Table 2-9. Levels of Significant Exposure to Polyalphaolefin Hydraulic Fluids - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/	System	NOAEL	LOAEL		Reference Fluid Identity
				Less Serious	Serious	
Rabbit (New Zealand)	24 hr	Bd Wt	1700 mg/kg			MacEwen and Vernot 1983 (DTNSRDC N518)
Rabbit (New Zealand)	24 hr	Bd Wt	1700 mg/kg			MacEwen and Vernot 1983 (DTNSRDC N448)
Rabbit (New Zealand)	once	Ocular	0.1 mL			MacEwen and Vernot 1983 (DTNSRDC N448)
Rabbit (New Zealand)	24 hr	Dermal	0.5 mL			MacEwen and Vernot 1983 (DTNSRDC N448)
Rabbit (New Zealand)	once	Ocular	0.1 mL			MacEwen and Vernot 1983 (DTNSRDC N501)
Rabbit (New Zealand)	24 hr	Bd Wt	1700 mg/kg			MacEwen and Vernot 1983 (DTNSRDC N501)
Rabbit (New Zealand)	24 hr	Dermal		0.5 mL	(mild skin irritant)	MacEwen and Vernot 1983 (DTNSRDC N501)
Rabbit (New Zealand)	24 hr	Dermal	0.5 mL			MacEwen and Vernot 1983 (DTNSRDC N525)
Rabbit (New Zealand)	once	Ocular	0.1 mL			MacEwen and Vernot 1983 (DTNSRDC N525)
Rabbit (New Zealand)	24 hr	Bd Wt	1700 mg/kg			MacEwen and Vernot 1983 (DTNSRDC N525)

Table 2-9. Levels of Significant Exposure to Polyalphaolefin Hydraulic Fluids - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/	System	NOAEL	LOAEL			Reference Fluid Identity
				Less Serious		Serious	
Rabbit (New Zealand)	24 hr	Bd Wt	1700 mg/kg				MacEwen and Vernot 1983 (DTNSRDC N527)
Rabbit (New Zealand)	24 hr	Dermal	0.5 mL				MacEwen and Vernot 1983 (DTNSRDC N527)
Rabbit (New Zealand)	24 hr	Bd Wt	1700 mg/kg				Kinkead et al. 1985 (MIL-H-83282)
Rabbit (New Zealand)	24 hr	Dermal	0.5 mL				Kinkead et al. 1985 (MIL-H-83282)
Rabbit (New Zealand)	once	Ocular	0.1 mL				Kinkead et al. 1985 (MIL-H-83282)
Rabbit (New Zealand)	once	Ocular		0.1 mL	(slight eye irritation)		Kinkead et al 1992b (MIL-H-83282LT)
Rabbit (New Zealand)	4 hr	Dermal	0.5 mL				Kinkead et al 1992b (MIL-H-83282LT)
Rabbit (New Zealand)	24 hr	Bd Wt	2000 mg/kg				Kinkead et al 1992b (MIL-H-83282LT)
Gn pig (Hartley)	9 d 4 x	Dermal		14 mg/ cm^2	M (erythema)		Kinkead et al. 1987b (B85-174)
Gn pig (Hartley)	2 d	Dermal	0.025 mL	0.05 mL	(mild irritation)		MacEwen and Vernot 1983 (DTNSRDC N501)

Table 2-9. Levels of Significant Exposure to Polyalphaolefin Hydraulic Fluids - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/	System	NOAEL	LOAEL		Reference Fluid Identity
				Less Serious	Serious	
Immunological/Lymphoreticular						
Gn pig (Hartley)	9 d 4x			14 mg/ cm^2	(skin sensitization in 4/10 guinea pigs)	Kinkead et al. 1987b (B85-174)
Gn pig (Hartley)	9 d 4 x		0.1 mL			MacEwen and Vernot 1983 (DTNSRDC N517)
Gn pig (Hartley)	9 d 4 x		0.1 mL			MacEwen and Vernot 1983 (DTNSRDC N518)
Gn pig (Hartley)	9 d 4 x		0.1 mL			MacEwen and Vernot 1983 (DTNSRDC N448)
Gn pig (Hartley)	9 d 4 x		0.025 mL			MacEwen and Vernot 1983 (DTNSRDC N501)
Gn pig (Hartley)	9 d 4 x		0.1 mL			MacEwen and Vernot 1983 (DTNSRDC N525)
Gn pig (Hartley)	9 d 4 x		0.1 mL			MacEwen and Vernot 1983 (DTNSRDC N527)
Gn pig (Hartley)	9 d 4 x		0.1 g			Kinkead et al. 1985 (MIL-H-83282)
Gn pig (Hartley)	8 d 4 x			0.1 mL	(dermal sensitization)	Kinkead et al. 1992b (MIL-H-83282LT)

Table 2-9. Levels of Significant Exposure to Polyalphaolefin Hydraulic Fluids - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/	System	NOAEL	LOAEL				Reference Fluid Identity
				Less Serious		Serious		
Neurological								
Rabbit (New Zealand)	24 hr			1700 mg/kg	(lethargy)			MacEwen and Vernot 1983 (DTNSRDC N517)
Rabbit (New Zealand)	24 hr			1700 mg/kg	(lethargy)			MacEwen and Vernot 1983 (DTNSRDC N518)
Rabbit (New Zealand)	24 hr			1700 mg/kg	(lethargy)			MacEwen and Vernot 1983 (DTNSRDC N448)
Rabbit (New Zealand)	24 hr			1700 mg/kg	(lethargy)			MacEwen and Vernot 1983 (DTNSRDC N501)
Rabbit (New Zealand)	24 hr			1700 mg/kg	(lethargy)			MacEwen and Vernot 1983 (DTNSRDC N525)
Rabbit (New Zealand)	24 hr			1700 mg/kg	(lethargy)			MacEwen and Vernot 1983 (DTNSRDC N527)

Bd Wt = body weight; d = day; F = female; Gn pig = guinea pig; hr = hour(s); LOAEL = lowest-observed-adverse-effect-level; M = male; NOAEL = no-observed-adverse-effect level; once = single dose or exposure; x = time(s)

2. HEALTH EFFECTS

No deaths occurred in rats after dermal exposure to Durad 220B, Durad 300, or Durad 110 under occluded conditions for 24 hours at dosage levels of 2,000 mg/kg (FMC 1990a). Dermal exposure to 2,890 mg/kg doses of a cyclotriphosphazene hydraulic fluid for 24 hours under occluded conditions likewise produced no deaths in rabbits (Kinkead et al. 1992c; MacEwen and Vemot 1985). Deaths associated with severe cholinergic symptoms and symptoms of delayed neuropathy occurred in a group of 50 cattle treated dermally with about 1.52 L of waste from reclamation of a Fyrquel hydraulic fluid (Julian et al. 1976). The material was poured over the backs of the animals as a ringworm treatment. Exposure was expected to have been by the oral route as well as by dermal contact, because the cows were seen licking their backs or the backs of other cows; 14 of 50 cows died within 4 weeks of exposure. The authors stated that this fluid may have been contaminated with tri-*ortho*-cresyl phosphate.

Johannsen and colleagues (1977) report dermal LD_{50} values for rabbits at levels of >3,700 mg/kg for a group of triaryl phosphates, >5,000 mg/kg for dibutyl phenyl phosphate, 5,000 mg/kg for both asymmetrical and symmetrical triaryls, and >3,100 mg/kg for tributyl phosphate. This study looked at structural activity relationships for the organophosphate esters.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding death in humans after dermal exposure to polyalphaolefin hydraulic fluids.

Several U.S. military polyalphaolefin hydraulic fluids (designated as B85-174, MJL-H-83282, MLL-H-83282, and DTNSBDC Nos. N448, N501, N5 17, N5 18, N525, and N527) produced no deaths in rabbits within 14 days of single 24-hour occluded exposures to either 2,000 mg/kg (B85-174 and MJL-H-83232LT) or 5 mL/kg (= 1,700 mg/kg; the remaining fluids were applied at this level) (Kinkead et al. 1987b; MacEwen and Vemot 1983). The test materials were spread evenly over the backs and sides of the animals.

2.2.3.2 Systemic Effects

The highest NOAEL and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Tables 2-7,2-8, and 2-9 for mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, and polyalphaolefin hydraulic fluids, respectively.

2. HEALTH EFFECTS

Respiratory Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding respiratory effects in humans or animals after dermal exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding respiratory effects in humans after dermal exposure to organophosphate ester hydraulic fluids.

Respiratory effects have been observed in one dermal toxicity study. Of six rabbits exposed to an unspecified amount of Cellulube 220 for an intermediate duration, one died on day 36 of weakness and dyspnea of 4%hour duration (Carpenter et al. 1959). Respiratory effects were not observed in rabbits dermally exposed to 1,000 mg/kg of cyclotriphosphazene for an intermediate duration (Kinkead et al. 1989c, 1990). No acute- or chronic-duration animal studies examining respiratory tract effects were located.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding respiratory effects in humans or animals after dermal exposure to polyalphaolefin hydraulic fluids.

Cardiovascular Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding cardiovascular effects in humans or animals after dermal exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding cardiovascular effects in humans after dermal exposure to organophosphate ester hydraulic fluids.

Several animal studies conducted histological examination of the heart following intermediate-duration dermal exposure to organophosphate ester hydraulic fluids. No cardiovascular effects were observed in rats exposed to 5,750 mg/kg/day of Fyrquel 220 (MacEwen and Vemot 1983), or rabbits exposed to 1,000 mg/kg/day of cyclotriphosphazene (Kinkead et al. 1989c, 1990) or an unspecified amount of Cellulube 220 (Carpenter et al. 1959).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding cardiovascular effects in humans or animals after dermal exposure to polyalphaolefin hydraulic fluids.

2. HEALTH EFFECTS

Gastrointestinal Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding gastrointestinal effects in humans or animals after dermal exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding gastrointestinal effects in humans after dermal exposure to organophosphate ester hydraulic fluids.

Diarrhea was observed in rabbits administered an unspecified amount of Cellulube 220 for an intermediate duration (Carpenter et al. 1959). Soft feces were also observed in *Pasturella*-infected rabbits receiving 5,750 mg/kg/day of Fyrquel220, but not 2,875 mg/kg for an intermediate duration (MacEwen and Vemot 1983). The diarrhea may have been the result of cholinesterase inhibition or of the underlying infection or a combination of the two. No gross or histological alterations were observed in rabbits receiving a dermal dose of 1,000 mg/kg/day of cyclotriphosphazene for an intermediate duration (Kinkead et al. 1989c, 1990).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding gastrointestinal effects in humans or animals after dermal exposure to polyalphaolefin hydraulic fluids.

Hematological Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding hematological effects in humans or animals after dermal exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No change in the levels of leukocytes was observed in workers dermally exposed to triaryl phosphate hydraulic fluids for an intermediate duration (Baldridge et al. 1959).

Two intermediate-duration studies examined hematological parameters (e.g., red blood cell levels, hemoglobin levels) following dermal exposure to organophosphate ester hydraulic fluid. No hematological effects were observed in rabbits exposed to 1,000 mg/kg/day of cyclotriphosphazene (Kinkead et al. 1989c, 1990) or in rabbits exposed to 5,750 mg/kg/day of Fyrquel 220 (MacEwen and Vemot 1983).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding hematological effects in humans or animals after dermal exposure to polyalphaolefin hydraulic fluids.

2. HEALTH EFFECTS

Musculoskeletal Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding musculoskeletal effects in humans or animals after dermal exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding musculoskeletal effects in humans after dermal exposure to organophosphate ester hydraulic fluids.

No gross or histological alterations in skeletal muscle were observed in rabbits exposed to 1,000 mg/kg/day of cyclotriphosphazene (Kinkead et al. 1989c, 1990) or in rabbits exposed to an unspecified amount of Cellulube 220 (Carpenter et al. 1959). Both of these studies were intermediate-duration dermal exposure studies. Studies examining musculoskeletal end points following acute- or chronic-duration exposure were not located.

Polyalphaolefm Hydraulic Fluids. No studies were located regarding musculoskeletal effects in humans or animals after dermal exposure to polyalphaolefin hydraulic fluids.

Hepatic Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding hepatic effects in humans or animals after dermal exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding hepatic effects in humans after dermal exposure to organophosphate ester hydraulic fluids.

In rabbit intermediate-duration studies, no gross or histological alterations in the liver were observed following exposure to 1,000 mg/kg/day of cyclotriphosphazene (Kinkead et al. 1989c, 1990) or an unspecified amount of Cellulube 220 (Carpenter et al. 1959), and no changes in liver weights Were observed in rabbits exposed to 5,750 mg/kg/day of Fyrquel 220 (MacEwen and Vemot 1983). No acute- or chronicduration studies examining hepatic end points were located.

Polyalphaolejin Hydraulic Fluids. No studies were located regarding hepatic effects in humans or animals after dermal exposure to polyalphaolefin hydraulic fluids.

2. HEALTH EFFECTS

Renal Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding renal effects in humans or animals after dermal exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding renal effects in humans after dermal exposure to organophosphate ester hydraulic fluids.

Significant increases in serum urea nitrogen and serum creatinine levels (which may be indicative of impaired renal function) were observed in Pasteurella-infected rabbits exposed to 2,875 or 5,750 mg/kg/day of Fyrquel220 for an intermediate duration (MacEwen and Vemot 1983). The results of the histological examination were not reported, and the renal effects of the infection were not discussed. No gross or histological alterations were observed in the kidneys of rabbits exposed to 1,000 mg/kg/day of cyclotriphosphazene (Kinkead et al. 1989c, 1990) or in rabbits exposed to an unspecified amount of Cellulube 220 for an intermediate duration (Carpenter et al. 1959). No studies examining renal effects following acute or chronic durations were located.

Polyalphaolejin Hydraulic Fluids. No studies were located regarding renal effects in humans or animals after dermal exposure to polyalphaolefin hydraulic fluids.

Endocrine Effects.

No studies were located regarding endocrine effects in humans or animals after dermal exposure to mineral oil or polyalphaolefin hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No histopathological evidence of adverse effects on the adrenal gland was found in rabbits dermally exposed to 1,000 mg/kg/day cyclotriphosphazene for 6 hours per day, 5 days per week, for 21 days (Kinkead et al. 1989c, 1990).

Dermal Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding dermal effects in humans after dermal exposure to mineral oil hydraulic fluids.

2. HEALTH EFFECTS

Several mineral oil hydraulic fluids have been shown to be skin irritants in rabbits following a single exposure. Moderate skin irritation, erythema, and edema were observed following application of a 0.5 mL napthenic petroleum-based hydraulic fluid designated as MIL-H-5606 (Kinkead et al. 1985). No signs of skin irritation were observed following application of 0.1 mL of Sunsafe F, Houghto-Safe 5047F, Quintolubric 95830W, or Pyroguard A-443 (Kinkead et al. 1987a, 1988).

Organophosphate Ester Hydraulic Fluids. Repeated application of a patch treated with 0.2 µL of Skydrol 500B-4 for 5 weeks (3 times/week) resulted in mild cumulative erythema confined to the contact site in 14 of 53 human test subjects, beginning with the third dose during the first week. No evidence of immediate primary dermal irritation was observed (Monsanto 1980).

Mild erythema and skin thickening was observed in rabbits following a single exposure to 0.5 mL of Durad 550B (FMC 1992a). A number of other animal studies have found no signs of skin irritation following acute exposure to Durad 220B (FMC 1990a), Durad 110 (FMC 1990a), Durad 300 (FMC 1990a), Durad MP280 (Gaworski et al. 1986; Kinkead et al. 1992d), Durad 125 (FMC 1991 b), Fyrquel 220 (Gaworski et al. 1986; Kinkead et al. 1992e), and cyclotriphosphazene (Gaworski et al. 1986; Kinkead et al. 1992a, 1992c; MacEwen and Vemot 1985). No evidence of skin histological damage was observed in rabbits repeatedly exposed to an unspecified amount of Cellulube 220 (Carpenter et al. 1959) or 1,000 mg/kg/day of cyclotriphosphazene (Kinkead et al. 1989c, 1990) for an intermediate duration. Skin irritation was not observed in rabbits exposed to 5,750 mg/kg/day of Fyrquel220 for an intermediate duration (MacEwen and Vemot 1983).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding dermal effects in humans after dermal exposure to polyalphaolefin hydraulic fluids.

A number of studies examined dermal end points in animals exposed to polyalphaolefin hydraulic fluids for an acute duration. Mild skin irritation was observed in rabbits following application of 0.5 mL of polyalphaolefin hydraulic fluids designated as DTNSRDC No. N50 1 or N5 17 (MacEwen andVemot 1983) and in guinea pigs following application of 0.05 mL DTNSRDC No. N501. No signs of dermal irritation were observed in rabbits following application of 0.5 mL of polyalphaolefin hydraulic fluids designated as DTNSRDC Nos. N448, N518, N525, and N527 (MacEwen and Vemot 1983), MIL-H-83282 (Kinkead et al. 1985), and MIL-H-83282LT (Kinkead et al. 1992b), and application of 142 mg/cm^2 of a polyalphaolefin hydraulic fluid with a Naval designation of B85-174 (Kinkead et al. 1987b).

2. HEALTH EFFECTS

Ocular Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding ocular effects in humans after exposure to mineral oil hydraulic fluids.

Mild eye irritation was observed following ocular application of 0.1 mL of Sunsafe F, Houghto-Safe 5047F, Quintolubric 95830W, or Pyroguard A-443 (Kinkead et al. 1987a, 1988). A NOAEL of 0.1 mL for eye irritation was identified for MIL-H-5606 (Kinkead et al. 1985). No longer term studies examining ocular end points were located.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding ocular effects in humans after exposure to organophosphate ester hydraulic fluids.

Eye irritation was not observed in animal studies following a single application of 0.1 mL of Fyrquel 220 (Gaworski et al. 1986; Kinkead et al. 1992e), Durad MP280 (Gaworski et al. 1986; Kinkead et al. 1992d), or cyclotriphosphazene (Kinkead et al. 1992c; MacEwen and Vemot 1985). Intermediate-duration exposure of rats, rabbits, or hamsters to aerosols of Fyrquel 220 or Durad MP280 (MacEwen and Vemot 1983), rabbits to Cellulube 220 (Carpenter et al. 1959), or rats to cyclotriphosphazene (Kinkead et al. 1989a, 1990) also did not cause eye irritation.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding ocular effects in humans after exposure to polyalphaolefin hydraulic fluids.

During a single 4-hour exposure to 1,120 mg/m^3 MIL-H-83282LT hydraulic fluid, rats showed signs of mucosal irritation including rubbing of the eyes and nose and squinting of eyes (Kinkead et al. 1992b). Exposure in this case was a whole-body exposure in an inhalation chamber and aerosols of the hydraulic fluid came into direct contact with the eyes. No other studies reported ocular effects following exposure to polyalphaolefin hydraulic fluid aerosols.

Eye irritation was observed in rabbits following ocular application of MIL-H-83282LT (Kinkead et al. 1992b). No signs of irritation were observed in rabbits following ocular application of 0.1 mL of polyalphaolefin hydraulic fluids designated as DTNSRDC Nos. N448, N501, N5 17, N5 18, N525, and N527 (MacEwen and Vemot 1983), MIL-H-83282 (Kinkead et al. 1985), or B85-174 (Kinkead et al. 1987b).

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Body Weight Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding body weight effects in humans after dermal exposure to mineral oil hydraulic fluids.

In acute toxicity studies, no significant changes in body weight were observed following dermal application of 2,000 mg/kg of Sunsafe F, Quintolubric 95830W, Houghto-Safe 5047F, Pyroguard A-443 (Kinkead et al. 1989b, 1988), or 1,800 mg/kg of a mineral oil hydraulic fluid meeting military specifications of MIL-H-5606 (Kinkead et al. 1985). No longer-term studies were located.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding body weight effects in humans after dermal exposure to organophosphate ester hydraulic fluids.

Following acute exposure, no changes in body weight gain were observed in rats exposed to 2,000 mg/kg of Durad 110, Durad 220B, or Durad 300 (FMC 1990a) or in rabbits exposed to 2,890 mg/kg of cyclotriphosphazene (Kinkead et al. 1992c; MacEwen and Vemot 1985). A transient weight loss was observed in rabbits exposed to 2 mL/kg of MIL-H-19457B or Fyrquel 220 (Gaworski et al. 1986; Kinkead et al. 1992a). Intermediate-duration exposure of rabbits to 1,000 mg/kg/day of cyclotriphosphazene (Kinkead et al. 1989c, 1990) or 5,750 mg/kg/day of Fyrquel 220 (MacEwen and Vemot 1983) did not alter body weight gains.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding body weight effects in humans after dermal exposure to polyalphaolefin hydraulic fluids.

No changes in growth were observed in rabbits following single applications of 1,700 mg/kg of polyalphaolefin hydraulic fluids designated as DTNSRDC N448, N501, N5 17, N5 18, N525, or N527 (MacEwen and Vemot 1983), 1,700 mg/kg of polyalphaolefin hydraulic fluids meeting military specifications of MIL-H-83282 (Kinkead et al. 1985) or 2,000 mg/kg of MIL-H-83282LT or B85-174 (Kinkead et al. 1992b). No longer-term studies were located.

2. HEALTH EFFECTS

2.2.3.3 Immunological and Lymphoreticular Effects

The highest NOAEL values and all LOAEL values for each reliable study for immunological effects in each species and duration category are recorded in Tables 2-7, 2-8, and 2-9 for mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, and polyalphaolefin hydraulic fluids, respectively.

Mineral Oil Hydraulic Fluids. No studies were located regarding immunological effects in humans after dermal exposure to mineral oil hydraulic fluids.

In guinea pig assays for skin sensitization, 4 of 5 tested mineral oil hydraulic fluids (Pyroguard A-443, Sunsafe F, Houghto-Safe 5047F, and MIL-H-5606) displayed no activity; the remaining fluid, Quintolubric 95830W, displayed only weak skin sensitization (skin sensitization occurred in only 1 of 10 guinea pigs) (Kinkead et al. 1985, 1987a, 1988). No other studies were located regarding immunological effects in animals after dermal exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No dermal sensitization was observed in a study of human subjects (46 females and 7 males) exposed dermally to 0.2 mL Skydrol 500B-4 for three 24-hour periods per week for 5 weeks (Monsanto 1980). No other studies were located regarding immunological effects in humans after dermal exposure to organophosphate ester hydraulic fluids. Two case reports of skin sensitization to triphenyl phosphate were found. A woman developed eczema from her eyeglasses containing the phosphate (Carlsen et al. 1986), and a carpenter tested positive to an allergy patch test, where a 5% petrolatum solution of triphenyl phosphate was applied after exposure to a glue containing it (Camarassa and Serra-Baldfich 1992).

No skin sensitization was seen in guinea pigs treated with four doses of 0.1 mL of a cyclotriphosphazenebased hydraulic fluid on the skin of the forelegs (Kinkead et al. 1992c; MacEwen and Vernot 1985). Thymus weight decreases (both absolute and relative to body weight) were observed, without histological alterations, in rabbits dermally exposed to 6-hour doses of cyclotriphosphazene ≤1,000 mg/kg, 5 days/week for 21 days (Kinkead et al. 1989c, 1990). No other studies regarding immunological effects in animals after dermal exposure were located.

2. HEALTH EFFECTS

Polyalphaolefin Hydraulic Fluids. No studies were located regarding immunological effects in humans after dermal exposure to polyalphaolefin hydraulic fluids.

Two U.S. military polyalphaolefin hydraulic fluids, MJL-H83232LT and B85-174, displayed skin sensitization activity in guinea pigs (Kinkead et al. 1987b, 1992b). Seven other polyalphaolefin hydraulic fluids did not produce skin sensitization in guinea pig assays; tested materials were designated as MIL-H-83282 (Kinkead et al. 1985) and DTNSDR Nos. N448, N501, N517, N518, N525, and N527 (MacEwen and Vernot 1983). No other studies were located regarding immunological effects in animals after dermal exposure to polyalphaolefin hydraulic fluids.

2.2.3.4 Neurological Effects

The highest NOAEL values and all LOAEL values for each reliable study for neurological effects in each species and duration category are recorded in Tables 2-7,2-8, and 2-9 for mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, and polyalphaolefin hydraulic fluids, respectively.

Mineral Oil Hydraulic Fluids. Weakness in the hands and the absence of tendon reflexes developed in a man whose skin was exposed heavily to mineral-oil-based hydraulic fluids on a daily occupational basis for ≈2 years. Reportedly, his hands and arms "were always wet with fluid," and his clothes were often saturated with fluid (Järvholm et al. 1986). The fluid, to which the man was exposed for an unspecified number of months prior to the appearance of neurotoxic signs, contained ≈0.5% isopropylated triphenyl phosphate and <50 ppm tri-*ortho*-cresyl phosphate (TOCP) according to the manufacturer's analysis. A coincidental association between polyneuropathy and exposure to hydraulic fluid in this case could not be excluded. Neurological examination of eight men who worked with mineral-oil-based hydraulic fluids for 3 months to 13 years revealed subtle electromyographical effects in several muscles of four of the men ("a reduced number of motor unit potentials"), but no such effects were observed in eight nonexposed male controls (Järvholm et al. 1986). Reportedly, the exposed men in this study were less heavily exposed to hydraulic fluids than the man who developed arm weakness and absence of tendon reflexes. The two reports provide limited evidence that dermal exposure to certain mineral-oil-based hydraulic fluids may produce neurological effects. Other studies on neurological effects in humans following dermal exposure to mineral-oil-based hydraulic fluids were not located.

2. HEALTH EFFECTS

In acute toxicity studies, rabbits exposed to 2,000 mg/kg occluded dermal doses of one of several mineral oil hydraulic fluids (Sunsafe F, Houghto-Safe 5047F, Quintolubric 95830W, Pyroguard A-443 and MIL-H-5606) for 24 hours displayed no signs of neurological toxicity within 14 days postdosing (Kinkead et al. 1985, 1987a, 1988). Other information on neurological effects in animals following dermal exposure to mineral oil hydraulic fluids was not located.

Organophosphate Ester Hydraulic Fluids. A brief overview of organophosphate ester neurotoxicity is presented in Section 2.2.1.4.

During a cleaning operation, 14 men on a U.S. Navy ship were dermally exposed on their hands and arms, and on the clothing to a hydraulic fluid described as a mixture of triphenyl phosphates (Baldridge et al. 1959). The men were directed to bathe and change clothing 24 hours after the operation. Blood samples were drawn for plasma and red blood cell cholinesterase measurement presumably 24 hours after the cleanup event and after an interval of 2 weeks. No significant differences in cholinesterase values were observed between theexposed men and a group of nonexposed men. The men were instructed to report the occurrence of any neuropathic symptoms to the medical department of the ship, but none were reported.

Another group of 14 men was exposed primarily by dermal contact to a triaryl phosphate hydraulic fluid during installation and operation of hydraulic aircraft elevators on a U.S. Navy ship (Baldridge et al. 1959). Neurological examinations, physical examinations, white blood cell counts, and blood cholinesterase measurements made several times during a 3- to 4-month operation period failed to detect differences between the exposed men and a group of eight nonexposed men from the same ship.

No other information was located regarding neurological effects in humans after dermal exposure to hydraulic fluids.

Several organophosphate ester hydraulic fluids produced no clinical signs of neurotoxicity in rats and rabbits during 14-day observation periods after 24-hour periods of occluded dermal exposure. Tested hydraulic fluids included Durad 110 (FMC 1990a), Durad 300 (FMC 1990a), and a cyclotriphosphazene-based hydraulic fluid (Kinkead et al. 1992c; MacEwen and Vemot 1985). These species are not susceptible to organophosphate-induced delayed neuropathy (Abou-Donia and Lapadula 1990).

2. HEALTH EFFECTS

Delayed neuropathy occurred in a group of 50 cattle after the waste from reclamation of contaminated hydraulic fluid was poured over their backs as a treatment for ringworms (Julian et al. 1976). The animals were observed licking their backs and the backs of others, suggesting that oral as well as dermal exposure occurred. The composition of the waste product was unknown, but the hydraulic fluid was identified as a Fyrquel that may have been contaminated with tri-*ortho*-cresyl phosphate (TOCP). The first signs of posterior weakness (knuckling at the fetlocks and mild ataxia) were noted 20 days after treatment. Decreased sensory and motor responses in the hind limbs were observed, and histopathological examination of seven cows revealed demyelination and degeneration in the spinal cord and the sciatic nerve.

Severe cholinergic signs (diarrhea, generalized weakness, dyspnea, and decreased blood cholinesterase activity) and subsequent death occurred in two rabbits given daily 4-hour occluded dermal exposures to Cellulube 220 that contained a mixture of tricresyl and trixylenyl phosphate esters (Carpenter et al. 1959). One rabbit died after 6 days of exposure and the other died after 42 days of exposure. Daily exposures of 1 or 2 hours also produced cholinergic signs in groups of two rabbits exposed for $\leq$44 days. One of the two rabbits exposed daily for 2 hours developed hind limb weakness with an altered gait. Histological examination of brain, spinal cord, and sciatic nerve tissues in exposed rabbits revealed no “remarkable” alterations. Although this study indicates that neurological effects occurred in rabbits with repeated dermal exposure to Cellulube 220, no dosage levels were reported. Neither clinical nor histopathological signs of neurotoxicity were observed in hens treated dermally with two doses of 5,000 mg/kg tributoxyethyl phosphate 21 days apart (Carrington et al. 1989)

A cyclotriphosphazene-based hydraulic fluid produced no deaths, signs of neurotoxicity or histological alterations in the brain or sciatic nerve in rabbits after occluded dermal exposure at 1,000 mg/kg/day, 6 hours/day (≈10% of body surface area), 5 days/week for 21 days (Kinkead et al. 1989c, 1990).

No other information was located regarding neurological effects in animals after intermediate to chronic dermal exposure to organophosphate ester hydraulic fluids.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding neurological effects in humans after dermal exposure to polyalphaolefin hydraulic fluids.

Information regarding neurological effects in animals after dermal exposure to polyalphaolefin hydraulic fluids is restricted to a report that lethargy was observed in some rabbits during 24-hour periods of exposure

to occluded topically applied (1,700 mg/kg) of polyalphaolefin hydraulic fluids designated as DTNSRDC Nos. N448, N501, N517, N518, N525, and N527 (MacEwen and Vemot 1983).

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after dermal exposure to mineral oil hydraulic fluids or to polyalphaolefin hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding reproductive effects in humans after dermal exposure to organophosphate ester hydraulic fluids.

Dermal exposure of male rabbits to unspecified doses of Cellulube 220 (14 hours/day, 4-5 days/week for ≤46 days) did not elicit histological alterations in the testes (Carpenter et al. 1959). Dermal exposure of male and female rabbits to cyclotriphosphazene at doses ≤1,000 mg/kg/day for 6 hours/day, 5 days/week, for 21 days did not affect the reproductive organs (Kinkead et al. 1989c, 1990). No other dermal studies examining reproductive effects in animals were located. This NOAEL value for reproductive effects in rabbits acutely exposed to cyclotriphosphazene hydraulic fluid is recorded in Table 2-8.

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after dermal exposure to mineral oil hydraulic fluids or to polyalphaolefin hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding developmental effects in humans after derrnal exposure to organophosphate ester hydraulic fluids.

After a single dermal exposure to waste from the reclamation of a Fyrquel hydraulic fluid that may have been contaminated with tri-*ortho*-cresyl phosphate (TOCP), no apparent signs of neurotoxicity wereobserved in calves of 10 cows that manifested neurotoxicity just after the birth of the calves. The cows were apparently also exposed orally concurrent to the dermal exposure (Julian et al. 1976). No intermediate- or chronic-duration dermal studies examining developmental effects in animals were located.

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2.2.3.7 Genotoxic Effects

Mineral Oil Hydraulic Fluids. No studies were located regarding genotoxic effects in humans or animals after dermal exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding genotoxic effects in humans or animals after dermal exposure to organophosphate ester hydraulic fluids. Genotoxicity studies for organophosphate ester hydraulic fluids are discussed in Section 2.5.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding genotoxic effects in humans or animals after dermal exposure to polyalphaolefin hydraulic fluids.

2.2.3.8 Cancer

Mineral Oil Hydraulic Fluids. A significant elevated odds ratio was found between stomach cancer and occupational exposure to hydraulic fluids in a case-control study examining associations between subjectively reported occupational exposure to petroleum-derived liquids and cancer in particular organs (Siemiatycki et al. 1987a). The reference group consisted of 2,514 cancer patients who did not have stomach cancer. The main group of patients (n=155) exposed to hydraulic fluids consisted of automotive mechanics exposed to transmission and brake fluids. While inhalation exposure was possible, dermal contact was the expected predominant exposure route. Although the association between exposure to hydraulic fluids and stomach cancer was statistically significant, the biological relevance is uncertain due to several limitations of the study including sample size, possible misclassification errors in subjective exposure assessment, and confounding exposure to other compounds. The importance of exposure to other chemicals as a limitation was emphasized by the authors' report that the association between stomach cancer and exposure to hydraulic fluids was no longer significant when adjustments were made for exposure to gasoline. No other information on cancer in humans exposed dermally to mineral oil hydraulic fluids was located.

No studies were located regarding cancer in animals after dermal exposure to mineral oil hydraulic fluids.

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Organophosphate Ester Hydraulic Fluids. No studies were located regarding cancer in humans or animals after dermal exposure to organophosphate ester hydraulic fluids.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding cancer in humans or animals after dermal exposure to polyalphaolefin hydraulic fluids.

2.3 TOXICOKINETICS

No studies were located that examined the toxicokinetics of mineral oil, organophosphate ester, or polyalphaolefin hydraulic fluids in humans or animals, with the exception of a study examining absorption in rats after exposure to a hydraulic fluid containing 99.9% cyclotriphosphazene (Kinkead and Bashe 1987) and the absorption and metabolism of Reolube HYD46, another organophosphate hydraulic fluid (Ciba-Geigy 1985). This section, therefore, discusses available information on the toxicokinetics of major components of these classes of hydraulic fluids or of materials that may be expected to display similar toxicokinetic properties based on similar physical and chemical characteristics. It should be emphasized that many hydraulic fluids are complex mixtures of chemicals that may include some chemicals which may not share toxicokinetic properties with the major components.

Hydrocarbons in mineral oil hydraulic fluids may be expected to be poorly absorbed, regardless of the route of exposure, based on results from studies with animals exposed to food-grade or medicinal mineral oil (Bollinger 1970; Ebert et al. 1966) or motor oil (Lushbaugh et al. 1950). Absorbed hydrocarbons from mineral oil are likely to be preferentially distributed to the liver and fatty tissues, slowly metabolized to various types of lipids (e.g., fatty acids or triglycerides), and excreted in the feces via the bile (Bollinger 1970; Ebert et al. 1966). Accumulation of oil in the lungs (and the consequent development of lipoid pneumonia), has been observed in humans and animals after inhalation or oral exposure to mineral oils (Cannon 1940; Lushbaugh 1950; Perrot and Palmer 1992).

No studies were located that examined the toxicokinetics of polyalphaolefins in humans or animals, but the similarities in physical and chemical properties between polyalphaolefins and hydrocarbons in mineral oil indicate that the toxicokinetics of polyalphaolefins may be similar to those of hydrocarbons in mineral oil hydraulic fluids.

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Animal studies with organophosphate esters, including tricresyl phosphate isomers (Abou-Donia et al. 1990a, 1990b; Casida et al. 1961; Eto et al. 1962; Kurebayashi et al. 1985; NTP 1988; Suwita and Abou-Donia 1990), isopropylated phenyl phosphates (Yang et al. 1990), and tributyl phosphate (Gatz 1992a, 1992b; Suzuki et al. 1984a) indicate that these compounds are readily absorbed by the gastrointestinal tract and may be absorbed by the skin (Ciba-Geigy 1985; Hodge and Sterner 1943; Nomeir and Abou-Donia 1986). Studies examining the toxicokinetics of inhaled aerosols of organophosphate esters were not located. Absorbed tricresyl phosphate isomers are widely distributed among animal tissues, and display a preferential distribution to fatty tissues, liver, and kidneys. They are readily cleared without displaying a tendency to accumulate (Abou-Donia et al. 1990a, 1990b; Hodge and Sterner 1943; Kurebayashi et al. 1985; Nomeir and Abou-Donia 1986; Somkuti and Abou-Donia 1990).

Animal studies with several organophosphate esters show that these compounds and their metabolites are excreted in the urine, bile, and feces. The relative importance of urinary versus fecal excretion appears to depend on the organophosphate ester and the dosage (NTP 1988; Somkuti and Abou-Donia 1990; Suzuki et al. 1984a). Species differences in sensitivity to experimental tri-*ortho*-cresyl phosphate-induced delayed neuropathy have been associated in part with apparently subtle differences among species in elimination kinetics (Abou-Donia 1990a, 1990b; Suwita and Abou-Donia 1990). (TOCP is not a hydraulic fluid, but a contaminant in older formulations of TCP-based hydraulic fluids.)

Metabolism of the triaryl and trialkyl organophosphate esters used in hydraulic fluids involves a very complex array of Phase I reactions including cytochrome P-450-mediated oxidations, dearylations, and cyclic rearrangements. For example, 19 metabolites were identified in rats after exposure to [^{14}C] labeled tributyl phosphate (Gatz 1992a). Phase II reactions include glutathione and glucuronic acid conjugations, as indicated by animal studies with several organophosphate esters including isopropylated phenyl phosphates (Yang et al. 1990), tri-*ortho*-cresyl phosphate (TOCP) (Abou-Donia 1990a, 1990b; Casida et al. 1961; Eto et al. 1962, 1967; Nomeir and Abou-Donia 1986; Somkuti and Abou-Donia 1990), tri-para-cresyl phosphate (Kurebayashi et al. 1985), and tributyl phosphate (Gatz 1992a, 1994; Suzuki et al. 1984a). The preferential distribution of radioactivity in the liver after administration of radiolabeled tricresyl phosphateisomers emphasizes the importance of the liver in metabolism of these compounds, but metabolism in other tissues is possible.

2. HEALTH EFFECTS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Mineral Oil Hydraulic Fluids. No studies were located regarding absorption in humans or animals after inhalation exposure to mineral oil hydraulic fluids.

Indirect evidence suggests that pulmonary absorption of hydrocarbons in mineral oil hydraulic fluids may occur. Mice, rats, and rabbits exposed to fogs (particle size ranged from 0.34 to 1.45 μm) of 63 mg/L of a diesel-engine lubricating oil for ≤343 days displayed (as indicated by histological analysis) oil in alveolar macrophages, mediastinal lymph nodes, lymphatic channels of the lungs, and in the pleura (Lushbaugh et al. 1950). A chemical analysis of lung and liver tissue found oil at respective concentrations of 0.13% and 0.03% (w/w) in exposed mice, but no oil in the same tissues from controls. These results are consistent with the hypothesis that mineral oil aerosols are not quickly absorbed by alveolar pneumocytes, and macrophages subsequently mediate clearance.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding absorption in humans after inhalation exposure to organophosphate ester hydraulic fluids.

No data were located regarding absorption in animals after inhalation exposure to organophosphate ester hydraulic fluids or specific organophosphate esters, except for the observation that parent material was not detected by gas chromatography in the blood or urine of male rats exposed to 5,120 mg/m^3 of an aerosol of a cyclotriphosphazene (99.9%) hydraulic fluid for 4 hours, thereby suggesting that the extent of absorption was limited (Kinkead and Bashe 1987). Blood samples were collected at 0,24, and 48 hours after exposure was terminated. Urine was collected for 24 hours after exposure.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding absorption in humans or animals after inhalation exposure to polyalphaolefin hydraulic fluids or their major components. Based on physicochemical similarities with mineral oils (i.e., long-chain aliphatic hydrocarbons are predominant components), inhaled aerosols of polyalphaolefin hydraulic fluids may enter the body by macrophagemediated clearance (see discussion above for mineral oil hydraulic fluids).

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2.3.1.2 Oral Exposure

Mineral Oil Hydraulic Fluids. No studies were located regarding absorption in humans or animals after oral exposure to mineral oil hydraulic fluids.

Food-grade or medicinal mineral oil, a mixture of aliphatic hydrocarbons that also may be found in mineral oil hydraulic fluids, is known to be absorbed only to a limited extent by the human gastrointestinal tract and has a laxative effect (Anonymous 1967; Brunton 1985), thus suggesting that mineral oil hydraulic fluids may behave likewise.

Experiments with rats given oral doses of tritiated food-grade mineral oil provide supporting evidence that the absorption of hydrocarbons in mineral oils is limited. Five hours after dosing with 0.66 mL/kg of tritiated mineral oil ("liquid petrolatum U.S.P."), ≈75% of the administered radioactivity remained in the alimentary tract, and only 3% of the administered radioactivity was accounted for by radioactivity in other parts of the rat carcass (Ebert et al. 1966). About 80% of the administered radioactivity was recovered in feces during the first 2 days after treatment, and over 90% of the radioactivity in the feces was in the form of mineral oil. These data are consistent with the hypothesis that ingested mineral oil was poorly absorbed. Neither biliary excretion nor enterohepatic circulation of mineral oils was measured in this study, and thus, any quantitative estimates of the extent of absorption based on these data should be viewed as tentative.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding absorption in humans or animals after oral exposure to organophosphate ester hydraulic fluids.

Studies of excretion in animals following oral administration of TOCP and tri-para-cresyl phosphate suggest that organophosphate esters found in hydraulic fluids may be extensively absorbed by the gastrointestinal tract (Abou-Donia et al. 1990a, 1990b; Kurebayashi et al. 1985; Suwita and Abou-Donia 1990).

One day after oral administration of single 7.8-mg/kg doses of [methyl-^{14}C]tri-para-cresyl phosphate (in DMSO) to male rats, radioactivity in urine, feces, expired air (as CO_2), and bile represented approximately 34%, 42%, 14%, and 28% of the administered dose, respectively (Kurebayashi et al. 1985). Measurements for expired air and excreted bile were carried out on five rats with cannulated bile ducts; fecal and urinary excretion were measured in another group of three rats without cannulated bile ducts. Assuming that radioactivity in urine, expired air, and bile represent absorbed compound, these results suggest that at least

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76% of the tri-para-cresyl phosphate dose was absorbed. In rats given larger single doses of [^{14}C]tri-para-cresyl phosphate (89.6 mg/kg), radioactivity in urine, feces, and expired air accounted for approximately 8%, 65%, and 3% of the dose, respectively, 1 day after dosing, and for 12%, 77%, and 6% of the dose, respectively, after 7 days. Enterohepatic circulation was not examined in the high-dose rats, but GC-MS analysis of the feces indicated that most of the radioactivity in the feces from the high-dose rats was unchanged tri-para-cresyl phosphate. This observation is consistent with the hypothesis that a significant portion of the high dose was not absorbed.

Male rats given single gavage doses of 50 mg/kg [uniformly labeled ^{14}C-phenyl]tri-*ortho*-cresyl phosphate in corn oil excreted approximately 50% and 25% of administered radioactivity in urine and feces, respectively, 24 hours after dosing (Abou-Donia et al. 1990a). Five days after dosing, cumulative radioactivity in urine and feces accounted for approximately 60% and 35%, respectively. Although biliary excretion and enterohepatic circulation were not examined in this study, the appearance of a large proportion of the administered radioactivity in the urine is indicative of extensive gastrointestinal absorption. Peak concentrations of radioactivity were observed between 2 and 48 hours after dosing (most tissues attained peak levels at 6 hours) in a number of nongastrointestinal tissues (Abou-Donia et al. 1990a); this implies that the TOCP was absorbed in less than 6 hours. The extent of absorption could not be estimated in companion excretion studies with chickens given single gavage doses of 50 mg/kg [uniformly labeled ^{14}C-phenyl]TOCP in corn oil, because chickens void urine and feces together and the authors did not attempt to separate them (Abou-Donia et al. 1990b; Suwita and Abou-Donia 1990). However, the hen studies provided qualitative evidence that TOCP was readily absorbed since radioactivity was detected within 12 hours of dosing in nongastrointestinal tissues including plasma, liver, kidney, and gall bladder.

Results from animal studies with other organophosphate esters also indicate ready gastrointestinal absorption. Rats given single oral doses of 14 mg/kg [1 -butyl-^{14}C]tributyl phosphate excreted approximately 50%, 10%, and 6% of applied radioactivity in urine, expired CO_2 and feces, respectively (Suzuki et al. 1984a). Metabolites of isopropylated phenyl phosphates were detected in the bile of rabbits within 6-24 hours of gavage administration of 2 g/kg Reolube HYD46, a hydraulic fluid containing isopropylated phenyl phosphates (Yang et al. 1990). Evidence for extensive absorption of tributyl phosphate was shown by the recovery of 66 to 80% of the radioactivity from [^{14}C]tributyl phosphate in urine for single oral doses up to 350 mg/kg in rats (Gatz 1992a, 1992b, 1994).

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Polyalphaolefin Hydraulic Fluids. No studies were located regarding absorption in humans or animals after oral exposure to polyalphaolefin hydraulic fluids.

As mentioned previously, ingested food-grade mineral oil is absorbed only to a limited extent in humans and animals (Brunton 1985; Ebert et al. 1966). The physicochemical similarities between polyalphaolefins and mineral oils suggest that the extent of gastrointestinal absorption of polyalphaolefin hydraulic fluids also may be limited.

2.3.1.3 Dermal Exposure

Mineral Oil Hydraulic Fluids. No studies were located regarding absorption in humans or animals after dermal exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. Limited studies indicate that organophosphate esters found in hydraulic fluids are absorbed by human skin. Radioactivity was detected in the blood and urine of two human subjects 1 hour after dermal exposure of both palms to 0.11 or 0.22 g of tri-*ortho*-cresyl phosphate labeled with radioactive phosphorus (Hodge and Sterner 1943). *In vitro* studies with human cadaver abdominal skin separating neat hydraulic fluids from an ethanol/water solution (70:30) found mean steady-state absorption rates of 0.9 and 0.54 μg/cm^2/hour for triphenyl phosphate (TPP) and 2-isopropylphenyl diphenyl phosphate (2-IDPP), respectively, from the hydraulic fluid additive Reofos 50 (Ciba-Geigy 1985). The Reofos 50 sample reportedly contained 261.5 mg/mL TPP and 341.43 mg/mL 2-IDPP. Using the hydraulic fluid, Reolube HYD46 (which contained 30.5 mg/mL TPP and 218.1 mg/mL 2-IDPP), steady-state absorption rates of 0.67 and 3.32 μg/cm2kour were measured for TPP and 2-IDPP, respectively. The applicability of these *in vitro* absorption rates to *in vivo* exposures is uncertain due to several limitations of the study, including the use of skin from only one individual, the use of 70% ethanol in the receptor chamber, and the absence of reference standards in the study.

Single dermal doses of 50 mg/kg tri-*ortho*-cresyl-[uniformly labeled ^{14}C-phenyl]phosphate (TOCP) were applied to preclipped, unprotected, 10-cm^2 areas of skin in male cats (Nomeir and Abou-Donia 1986). Three treated cats were sacrificed 0.5, 1,2,5, and 10 days after treatment. Radioactivity in urine and feces collected over the 10-day period accounted for 28% and 19% of the applied dose, respectively, but no radioactivity was detected in expired air. Radioactivity in analyzed tissues reached maximal levels at 24 hours (accounting for 8.7% of the applied dose). These data are inadequate for quantitative measurements of the extent of dermal

absorption of TOCP, because a significant fraction of the applied radioactivity was not accounted for in the analysis, and some of the TOCP may have been ingested by the cats during grooming.

Radioactivity was detected in the blood and urine of a single female dog, 1 hour after dermal application of a 2.094-g dose of TOCP labeled with radioactive phosphorus to a 300-cm^2 area of clipped and depilated abdominal skin (Hodge and Sterner 1943). Gas chromatographic analysis of blood detected no parent material in male rats at 4,24, or 48 hours after a 24-hour, occluded exposure to a hydraulic fluid containing 99.9% cyclotriphosphazene, but the presence of metabolites in the blood was not investigated (Kinkead and Bashe 1987).

In Yucatan minipigs dermally exposed for 6 hours to 350 mg/kg, [^{14}C]tributyl phosphate was only poorly absorbed (less than 5% of the applied dose). Absorption in rats treated under similar conditions was much higher (54-58%) (Gatz 1992a, 1992b).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding absorption in humans or animals after dermal exposure to polyalphaolefin hydraulic fluids.

2.3.1.4 Other Routes of Exposure

Mineral Oil Hydraulic Fluids. Absorption of a mineral oil in an emulsion was apparently very slow in female rats injected subcutaneously with 0.1 mL and in squirrel monkeys injected intramuscularly with 0.3 mL (Bollinger 1970). The emulsion contained 1 volume mannide monoleate, 9 volumes mineral oil, and 9 volumes water; [^{14}C] labeled hexadecane, a major component of the mineral oil, was added to the emulsion as a radiotracer. At 1 week and 10 months after treatment, radioactivity remaining at the sites of injection accounted for 85-99% and 25-33%, respectively, of the administered radioactivity.

Organophosphate Ester Hydraulic Fluids. Absorption rates of TOCP were measured in chickens after subcutaneous injection by measuring the apparent disappearance of TOCP from the site of injection with ^{31}P NMR spectroscopy (Carrington et al. 1988). Five chickens were injected with single, 1 ,187-mg/kg, neurotoxic doses in the back of the neck. Diminishment of the ^{31}P-TOCP signal at the site of injection showed a biphasic pattern; calculated half-lives for the first and second phases were 3.22 hours and 15.3 days. The authors interpreted the first phase to be indicative of spreading of the material under the skin

and the second phase to be indicative of absorption. They concluded that absorption of the subcutaneously injected material was slow.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding absorption of polyalphaolefin hydraulic fluids in humans or animals after exposure by routes other than inhalation, oral, or dermal.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Mineral Oil Hydraulic Fluids. No studies were located regarding distribution in humans or animals after inhalation exposure to mineral oil hydraulic fluids.

Numerous case reports of lipoid pneumonia in humans exposed through intranasal application of liquid petrolatum in medicinal nose drops (Cannon 1940; Lushbaugh et al. 1950) suggest that accumulation of oil in the lungs may be a concern with prolonged or high-level exposure to aerosols of mineral oils in hydraulic fluids. An examination of mice exposed to fogs of a lubricating oil for ≤343 days chemically detected oil in lung (0.13% [w/w]) and liver (0.03% [w/w]) tissue and histologically detected oil in alveolar macrophages, mediastinal lymph nodes, and lymphatic channels of the lung (Lushbaugh 1950). Further information regarding the distribution of inhaled mineral oil was not located.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding distribution in humans or animals after inhalation exposure to organophosphate hydraulic fluids.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding distribution in humans or animals after inhalation exposure to polyalphaolefin hydraulic fluids.

Oil accumulationin the lungs after long-term or high-level exposure to aerosols of polyalphaolefin may be a concern, based on observations of lipoid pneumonia in humans after prolonged intranasal application of mineral oil mists (Lushbaugh 1950) and the physical and chemical similarities between mineral oil and polyalphaolefins (i.e., both are composed predominately of aliphatic hydrocarbons).

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2.3.2.2 Oral Exposure

Mineral Oil Hydraulic Fluids. No studies were located regarding distribution in humans or animals after oral exposure to mineral oil hydraulic fluids.

Limited evidence suggests that oil accumulation in the lungs may occur due to aspiration of ingested mineral oil hydraulic fluids. Although the danger of aspiring mineral oil into the lungs is not as great as other petroleum-based hydrocarbon mixtures with higher volatility and lower viscosity such as kerosene (Gerarde 1963; Klein and Simon 1986), oil accumulation in the lungs and lipoid pneumonia were observed in a child who ingested approximately 5-10 mL of a mineral oil automobile transmission fluid (Perrot and Palmer 1992).

Mineral oil may accumulate to some degree in liver and fatty tissues after absorption of ingested mineral oil hydraulic fluids, as indicated by experiments with rats given single, 0.66-mL oral doses of tritiated mineral oil (Ebert et al. 1966). Twenty-four hours after administration, the concentrations of tritiated mineral oil in liver and fat were approximately seven-fold greater than those in kidney and brain; other tissues were not examined.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding distribution in humans or animals after oral exposure to organophosphate ester hydraulic fluids.

A triaryl phosphate ester, tributoxyethyl phosphate, was detected at a mean concentration of 11.3 ng/g in 41 of 115 human adipose tissue samples taken from cadavers from Kingston and Ottawa, Canada (LeBel and Williams 1986). Because triaryl phosphate esters have been found in Canadian drinking water and fish, the presumed route of exposure of these individuals was oral. This study provides limited evidence that organophosphate esters found in hydraulic fluids may accumulate in human fatty tissue.

Studies with rats and chickens given oral doses of TOCP and tri-*para*-cresyl phosphate provide more definitive evidence that, following absorption, organophosphate esters in hydraulic fluids (or their metabolites) may be widely distributed among tissues with a preferential distribution to fatty tissues, the liver, and the kidneys (Abou-Donia et al. 1990a, 1990b; Kurebayashi et al. 1985; Somkuti and Abou-Donia 1990; Suwita and Abou-Donia 1990).

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Less than 1% of total radioactivity was found in tissues 6-48 hours after oral administration of [^{14}C]tributyl phosphate. The majority of label was found in urine (70%) and feces (18%) after both single and multiple doses of 10 and 350 mg/kg/day (Gatz 1992b). Approximately 5% of the label was recovered as CO_2 in expired air.

Twenty-four hours following oral administration of 89.6 mg/kg of [methyl-^{14}C]tri-*para*-cresyl phosphate to male rats, radioactivity was detected in all tissues examined (Kurebayashi et al. 1985). Aside from the stomach and intestines, the highest concentrations (in units of ug-equivalents per gram of tissue) were found in fatty tissue (20), liver (1 l), and kidney (4). Radioactivity was detected at lower concentrations (>0.2 and <2 μg-equivalents per gram of tissue) in the following tissues listed in order of decreasing concentration: lungs, spleen, thymus, blood, testicles, heart, muscle, and brain. In male rats given single oral doses of 50 mg/kg [uniformly labeled ^{14}C-phenyl]TOCP, peak concentrations of radioactivity were observed between 2 and 48 hours after dosing (most tissues attained peak levels at 6 hours) in the following nongastrointestinal tissues, listed in order of decreasing concentration: urinary bladder, adipose tissue, liver, kidney, plasma, lungs, red blood cells, sciatic nerve, heart, spleen, testes, brain, spinal cord, and muscle (Abou-Donia et al. 1990a). The high concentration of radioactivity in the urinary bladder suggests that urinary excretion was significant (see Section 2.3.4). Similar evidence for widespread distribution of TOCP with preferential distribution to fat, liver, and kidneys was found in experiments in which male rats were given 10 daily doses of 50 mg/kg [uniformly labeled ^{14}C-phenyl]TOCP (Somkuti and Abou-Donia 1990) and chickens were given single oral doses of 50 mg/kg [uniformly labeled ^{14}C-phenyl]TOCP(Abou-Donia et al. 1990b).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding distribution in humans or animals after oral exposure to polyalphaolefin hydraulic fluids.

Based on physical and chemical similarities between mineral oil and polyalphaolefins, oil accumulation in the lung (and subsequent lipoid pneumonia) may occur following the ingestion of polyalphaolefin hydraulic fluids due to aspiration, and that distribution of polyalphaolefins to the liver and fatty tissues may occur to some degree (see-discussion for distribution of mineral oil hydraulic fluids).

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2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to mineral oil or polyalphaolefin hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding distribution in humans after dermal exposure to organophosphate ester hydraulic fluids.

A study with a dog exposed to an occluded dermal dose of TOCP labeled with radioactive phosphorus provides limited evidence that organophosphate esters in hydraulic fluids may be widely distributed after dermal absorption (Hodge and Sterner 1943). Similar widespread distribution of radioactivity among tissues was observed in male cats after dermal exposure to [uniformly labeled ^{14}C-phenyl]TOCP (Nomeir and Abou-Donia 1986). Tissues and fluids with the highest concentrations of radioactivity in these studies included the bile, gall bladder, urinary bladder, liver, kidney, and fat, thus suggesting that TOCP and metabolites are somewhat preferentially distributed to these tissues.

Twenty-four hours after application of 2.094 g TOCP labeled with radioactive phosphorus to a 15x20 cm area of clipped and depilated abdominal skin, radioactivity was detected in the following tissues in a dog, listed in order of decreasing concentration (counts per gram of tissue): skin and facia at site of application, liver, omental fat, blood, kidney, lung, muscle (triceps femoris), spinal cord, heart, spleen = brain = sciatic nerve, and bone (femur) (Hodge and Sterner 1943).

In male cats, peak concentrations of radioactivity in most tissues and fluids were observed 24 hours after application of 50 mg/kg [uniformly labeled ^{14}C-phenyl]TOCP to unprotected areas of skin on the back of the neck (Nomeir and Abou-Donia 1986). Peak concentrations of radioactivity (reported in parentheses in units of μg TOCP equivalent per gram) were highest for collected bile (317), followed by gall bladder (39.7), urinary bladder (39.1), kidneys (25.3), liver (16.3), cecum (14.5), fat (12.0), plasma (12.1), and lungs (12.1). Radioactivity was also detected in the following cat tissues (listed in order of decreasing concentration) but at peak concentrations <10 ug TOCP equivalents per gram: large intestine, sciatic nerve, red blood cells, pancreas, small intestine, heart, stomach, muscle, spleen, brain, and spinal cord. The observation of radioactivity in the stomach suggests that cats in his study ingested TOCP during grooming.

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2.3.3 Metabolism

Mineral Oil and Polyalphaolefin Hydraulic Fluids. No studies were located regarding metabolism in humans or animals after exposure to mineral oil hydraulic fluids or polyalphaolefin hydraulic fluids. It should be noted, however, that hydrocarbons found in mineral oils generally are not expected to undergo extensive metabolism in animals or humans (Cannon 1940; IARC 1984). It may be speculated that polyalphaolefins may undergo limited metabolism of a similar nature.

Experiments with monkeys given intramuscular injections of a mineral oil emulsion with [1 -^{14}C]n-hexadecane tracer provide data illustrating that absorbed C-16 hydrocarbon (a major component of liquid petrolatum) is slowly metabolized to various classes of lipids (Bollinger 1970). Two days after injection, substantial portions of the radioactivity recovered in liver (30%), fat (42%), kidney (74%), spleen (8 l%), and ovary (90%) were unmetabolized n-hexadecane. The remainder of the radioactivity was found as phospholipids, free fatty acids, triglycerides, and sterol esters. Essentially no radioactivity was found in the water-soluble or residue fractions. One or three months after injection, radioactivity still was detected only in the fat-soluble fractions of the various organs, but 80-98% of the detected radioactivity was found in non-hydrocarbon lipids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding metabolism in humans after exposure to organophosphate ester hydraulic fluids.

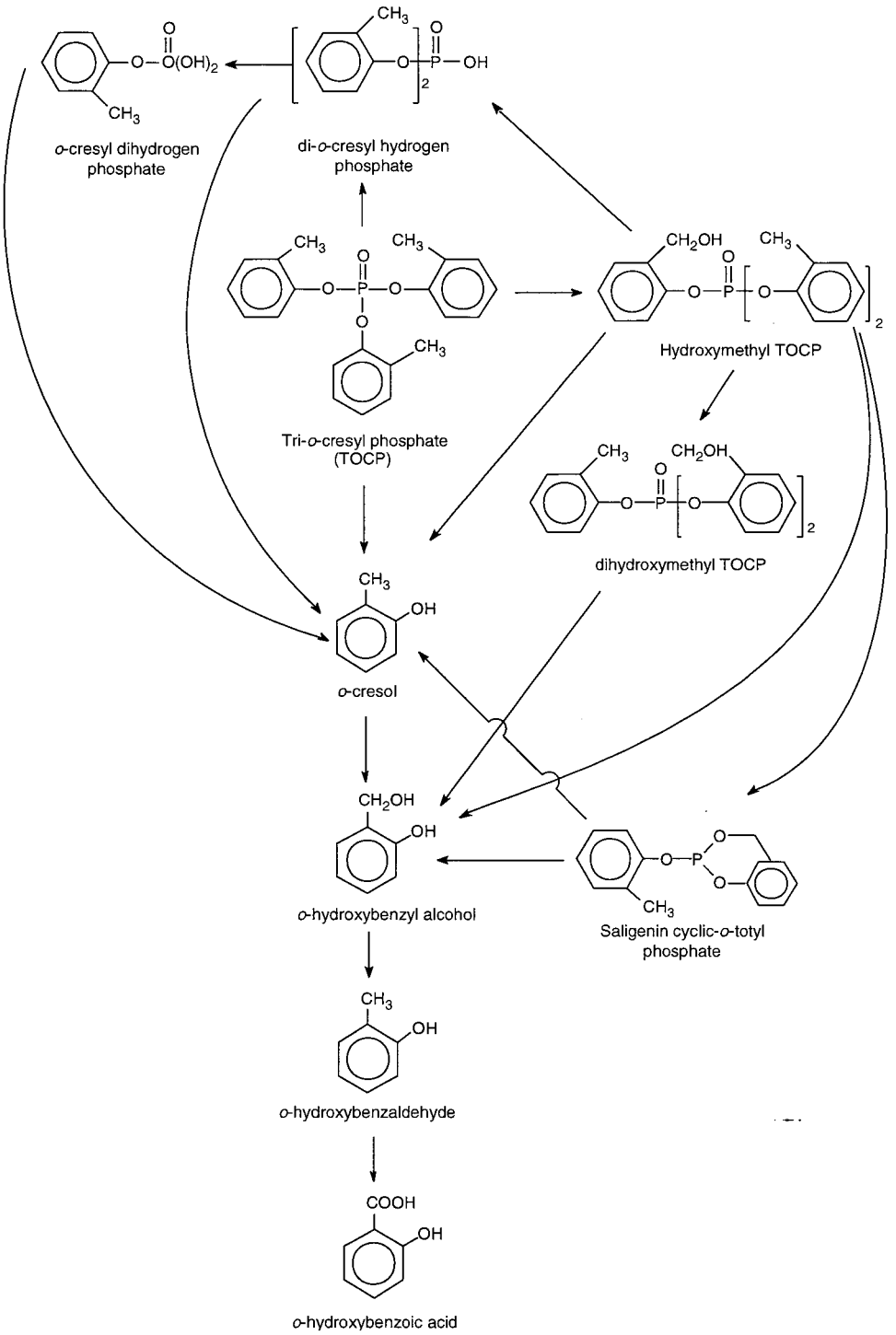
Studies directly examining the metabolism of organophosphate ester hydraulic fluids in animals are limited. One study identified metabolites in ether extracts of bile obtained from rabbits given single, 2 g/kg, oral doses of Reolube HYD46, a hydraulic fluid containing isopropylated triphenyl phosphates (35% mono-[o-isopropylphenyll-diphenyl phosphate, 25% di-[*o*-isopropylphenyll-phenyl phosphate, 10% tri-[o-isopropylphenyl] phosphate, and 7% triphenyl phosphate) (Yang et al. 1990). Metabolites were identified by mass spectrometry. Identified metabolites in extracts treated with ß-glucuronidase included isopropylated triphenyl phosphate derivatives hydroxylated at either the phenyl group or the isopropyl group. This finding is consistent with the hypothesis that Phase I oxidation reactions took place (presumably catalyzed by microsomal cytochrome P-450 mixed function oxidases) followed by Phase II glucuronic-acidconjugation reactions. Two cyclic metabolites (in which only two of the original three phenyl groups remained) were identified in bile extracts without ß-glucuronidase treatment (Yang et al. 1990). This finding is consistent with the *in vivo* occurrence of cyclization reactions that split off one of the phenyl groups (which

presumably leaves as phenol) and form a six-membered heterocyclic ring involving the *α*-carbon of the isopropyl residue on one of the remaining phenyl groups. These reactions are similar to those proposed to occur in the metabolism of TOCP (discussed in the next paragraph). No studies were located that definitively identify the enzymes involved in the formation of isopropylated triphenyl phosphate metabolites or their distribution among organs and within cells.

The metabolism of TOCP has received considerable study because tricresyl phosphate isomers are widely used as plasticizers, flame retardants, and lubricants. TOCP is also widely used in mechanistic studies of organophosphate ester-induced neurotoxicity in animals. Cholinergic and delayed neuropathic responses to TOCP in humans are well known, and TOCP metabolism has been related to its biological activity (Casida et al. 1961). Definitive *in vivo* and *in vitro* evidence for the participation of hydroxylation reactions and cyclization reactions (hydrolytic dearylation and cyclic rearrangements) in metabolism of TOCP was first presented for the rat (Eto et al. 1962, 1967). A particular cyclic metabolite, saligenin cyclic-*ortho*-tolyl phosphate, is generally thought to be the responsible agent for TOCP-induced delayed neuropathy. The metabolic production of this metabolite, however, does not necessarily predict the occurrence of delayed neuropathy, since it can be detected in various tissues (including brain tissue) in the rat, a species that does not display the classical symptoms of delayed neuropathy as seen in humans (Baron 1981; Casida et al. 1961; Eto et al. 1962; Somkuti and Abou-Donia 1990).

A recent series of experiments with cats, chickens, or rats exposed to [uniformly labeled ^{14}C-phenyl]-TOCP shows that a complex array of oxidized and dearylated metabolites are found in excreta and various tissues including the liver, kidney, testis, and brain (Abou-Donia et al. 1990a, 1990b; Nomeir and Abou-Donia 1986; Somkuti and Abou-Donia 1990). Cats and chickens, like humans, are sensitive to TOCP-induced delayed neuropathy (Baron 1981). A similar array of oxidized and dearylated derivatives of tri-*para*-cresyl phosphate (but no cyclic metabolites) were identified by mass spectrometry in the urine and bile of rats orally exposed to tri-*para*-cresyl phosphate (Kurebayashi et al. 1985). In contrast to TOCP, tri-*para*-cresyl phosphate does not cause delayed neuropathy. The identified metabolites suggest that the metabolism of tricresyl phosphate isomers involves a complex array of Phase I and Phase II reactions including oxidations of the methyl and phenyl groups (to produce alcohols, aldehydes, and carboxylic acids, presumably via cytochrome P-450 mixed function oxidases), hydrolytic dearylations, cyclic rearrangements (for TOCP derivatives only), and conjugations with glucuronic acid or glutathione. A metabolic pathway for TOCP as proposed by Somkuti and Abou-Donia (1990) is illustrated in Figure 2-7.

Figure 2-7. Metabolic Pathway for Tri-*ortho*-Cresyl Phosphate (TOCP)



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Eleven metabolites of [butyl-l-^{14}C]tributyl phosphate, an organophosphate ester used as a base stock in some aircraft hydraulic fluids (WHO 1991), were identified in urine from rats given single 250-mg/kg intraperitoneal injections of the compound (Suzuki et al. 1984a). Major metabolites included dibutyl hydrogen phosphate, butyl dihydrogen phosphate, and butyl bis(3-hydroxybutyl)phosphate. Several sulfurcontaining metabolites also were also identified in urine including (3-oxobutyl)- and (3-hydroxybutyl)-mercapturic acids (Suzuki et al. 1984b). Two hours after administration of 1 mmole tributyl phosphate, levels of glutathione diminished to 55% and 75% of initial levels in liver and kidney, respectively (Suzuki et al. 1984b). Based on these data, a complex metabolic scheme for tributyl phosphate has been proposed involving mixed function oxidase-mediated oxidations of the butyl groups and glutathione-S-transferase-mediated transalkylations (Suzuki et al. 1984b). Similarly complex metabolite profiles (19 metabolites) for tributyl phosphate after oral, dermal, and intravenous administration have also been seen in rats (Gatz 1992b).

The preferential (although not exclusive) distribution of radioactivity to the liver and kidneys after dermal (Nomeir and Abou-Donia 1986) and oral (Abou-Donia et al. 1990a, 1990b; Kurebayashi et al. 1985; Somkuti and Abou-Donia 1990; Suwita and Abou-Donia 1990) exposure of cats, rats, and chickens to radiolabeled tricresyl phosphate isomers suggests that these organs may play important roles in the metabolism of organophosphate esters found in hydraulic fluids. Existing demonstrations of *in vitro* metabolism of TOCP with liver preparations emphasize the role of the liver (Casida et al. 196 1; Eto et al. 1962). It is possible, however, that metabolism occurs at other sites, including the gastrointestinal tract and the testes. In rats given oral doses of [methyl-^{14}C]tri-para-cresyl phosphate, 18% of the administered radioactivity was exhaled after 3 days as CO_2: if rats were pretreated with neomycin, then expiration of radiolabeled CO_2 decreased to 3% of the administered dose (Kurebayashi et al. 1985). The neomycininduced decrease in expired radioactivity suggests that a small, but measurable, portion of orally administered triaryl phosphates may be metabolized by gut microflora. Cultured Leydig cells from rat testes could metabolize TOCP to saligerin cyclic-*o*-tolyl phosphate (Chapin et al. 1990).

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2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding elimination and excretion in humans or animals after inhalation exposure to mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, or to polyalphaolefin hydraulic fluids.

2.3.4.2 Oral Exposure

Mineral Oil Hydraulic Fluids. No studies were located regarding excretion in humans or animals after oral exposure to mineral oil hydraulic fluids.

Experiments with rats given oral or intraperitoneal doses of tritiated mineral oil (Liquid Petrolatum USP) indicate that orally administered hydrocarbons in mineral oil are predominately excreted rapidly, unchanged, and unabsorbed in the feces and that absorbed mineral oil is slowly excreted in the feces (presumably via biliary excretion) (Ebert et al. 1966).

Approximately 80% of administered radioactivity was excreted in the feces of rats within 2 days of oral administration of single 0.66 mL/kg doses of tritiated mineral oil (Ebert et al. 1966). Of administered radioactivity, 7-8% was excreted in the urine, but was in chemical forms other than mineral oil. The fecal radioactivity was predominately (90%) in the form of mineral oil. Pretreatment of the rats with 0.66 ml/kg/day nonradioactive mineral oil for 3 1 days did not substantially alter the excretion patterns.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding excretion in humans after oral exposure to organophosphate ester hydraulic fluids.

Studies with rats treated orally with triaryl or trialkyl phosphate esters (which may be found in organophosphate ester hydraulic fluids) indicate that these compounds and their metabolites are readily excreted in the urine, bile, feces and, to a limited extent, in expired air (Kurebayashi et al. 198.5; Somkuti and Abou-Donia 1990a; Suzuki et al. 1984a; Yang et al. 1990). Urinary excretion of metabolites appears to be the predominant elimination route in rats for tri-*ortho*-cresyl phosphate and tri-*para*-cresyl phosphate, but biliary excretion of parent material and metabolites is also important (Kurebayashi et al. 1985; NTP 1988). Fecal excretion may gain relative importance as an excretory route for tri-*para*-cresyl phosphate as doses

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approach levels of ≈100 mg/kg (Kurebayashi et al. 1985; NTP 1988). Fecal excretion of tri-*m*-cresyl phosphate appears to be predominant in rats even at a dose level of 200 mg/kg (NTP 1988).

In rats gavaged with 7.8 mg/kg [methyl-^{14}C]tri-*para*-cresyl phosphate, most administered radioactivity was excreted in the urine (41%) and feces (44%) within 7 days of administration (Kurebayashi et al. 1985). Biliary excretion was estimated using a separate group of rats with cannulated bile ducts to account for -28% of administered dose. CO, in expired air accounted for 18% of administered radioactivity, but this diminished to 3% when the rats were pretreated with the antibiotic, neomycin (thereby indicating that some of the compound was metabolized by the gut microflora). Fecal excretion was relatively more important than urinary excretion after administration of a higher dose, 89.6 mg/kg tri-*para*-cresyl phosphate (77% versus 12% of administered radioactivity, respectively). Unchanged tri-*para*-cresyl phosphate was reported to be the main fecal "metabolite," thereby indicating that absorption may have been incomplete at the higher dose. Half-lives of radioactivity in tissues were reported to range from 14 hours for blood to 26 hours for lungs and brain.

In rats given 10 daily 50-mg/kg doses of [phenyl-^{14}C]TOCP, 63.1% and 36.1% of administered radioactivity was excreted in the urine and feces, respectively, within 4 days of the last administration (Somkuti and Abou-Donia 1990a). Most of the radioactivity in urine was in metabolites found in an acid hydrolysate fraction, emphasizing the importance of Phase II metabolism in the disposition of TOCP (see Section 2.3.3). Major metabolites in feces included (in order of decreasing abundance) o-cresol, unchanged TOCP, "unknowns," and o-hydroxybenzoic acid. The authors reported that TOCP concentrations in brain, liver, kidney, testis, and plasma decreased exponentially within 4 days of the last dosing; estimated half-lives ranged from approximately 12 hours (0.49 days) in brain tissue to 24 hours (0.98 days) in the liver. The authors did not calculate half-lives for total radioactivity in tissues or plasma, but in a related study, the same group of investigators reported that the approximate half-life of radioactivity in tissues in general was 1 day in rats treated with single doses of 50 mg/kg [phenyl-^{14}C]TOCP (Abou-Donia et al. 1990a).

Patterns of excretion in rats differed among [^{14}C]labeled tricresyl phosphate isomers administered by gavage at dosage levels ranging from 0.5 to 200 mg/kg (NTP 1988). Radioactivity from tri-*ortho*-cresyl phosphate was excreted within 24 hours predominately in urine at all dosage levels (270% of applied doses). Radioactivity from tri-*m*-cresyl phosphate was excreted predominately in feces at all dosage levels. In contrast, urinary excretion of radioactivity from tri-*para*-cresyl was the predominant excretory route at low doses (0.5 or 2 mg/kg), while fecal excretion was the primary route at higher doses (20 or 200 mg/kg).

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Male rats given single, oral doses of 14 mg/kg [l-^{14}C]tributyl phosphate excreted 50% of the label in urine, 10% in exhaled air as $CO_2$and 6% in the feces within 1 day (Suzuki et al. 1984a). Within 5 days, cumulative radioactivity in urine, exhaled $CO_2$and feces accounted for approximately 68%, 10%, and 10% of the administered radioactivity, respectively.

Studies with chickens treated with single oral doses of 50 mg/kg [phenyl-^{14}C]TOCP provide general corroborative data for the ready excretion of TOCP and metabolites (Abou-Donia et al. 1990b; Suwita and Abou-Donia 1990). However, the relative importance of urinary and fecal excretion cannot be ascertained from these studies, because feces and urine were not separated. Approximately 47% of administered radioactivity was found in excreta by 12 hours after administration; radioactivity in excreta collected for 5 days accounted for 99% of administered radioactivity (Abou-Donia et al. 1990b). Plasma half-lives of TOCP and saligenin cyclic-*ortho*-tolyl phosphate, the putative neurotoxic agent in TOCP, were reported to be 53 and 46 hours, respectively, and were compared with respective values of 46 and 19 hours for plasma half-lives in rats treated with single doses of [phenyl-^{14}C]TOCP at the same dosage level (Abou-Donia 1990a). The authors suggested that the clearance of TOCP and its metabolites in plasma and tissues is slower in the hen (which is sensitive to TOCP-induced delayed neuropathy) than in the rat (which is less sensitive) and that this apparent difference may contribute to the difference in responses between these species (Abou-Donia 1990a, 1990b; Suwita and Abou-Donia 1990).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding excretion in humans or animals after oral exposure to polyalphaolefin hydraulic fluids or major components. The physicochemical similarities between polyalphaolefins and mineral oils suggest that hydrocarbons in ingested polyalphaolefins may be excreted similarly to hydrocarbons in ingested mineral oil.

2.3.4.3 Dermal Exposure

Mineral Oil Hydraulic Fluids. No studies were located regarding excretion in humans or animals after dermal exposure to mineral oil hydraulic fluids or to their major components. -.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding excretion in humans after derrnal exposure to organophosphate ester hydraulic fluids. However, a human study using the tricresyl phosphate isomer tri-o&o-cresyl phosphate (TOCP) was located.

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Urinary excretion of radioactivity was measured in human volunteers during and after a 3.5-hour period of dermal exposure to 0.11 or 0.22 g ^{32}P-labeled TOCP (Hodge and Sterner 1943). The specific activity of the test substance was not reported. Radioactivity in urine was measured with a Geiger-Muller counter, but the limits of detection were not reported. Maximum estimated excretion rates, 10 and 43 ug TOCP/hour for the respective dosage levels, were measured within 24 hours of initiation of exposure. Radioactivity was not detected 48 or 72 hours after dosing ceased. Cumulative radioactivity detected in urine accounted for 0.13% and 0.36% of the dermally applied radioactivity.

Cyclotriphosphazene was not detected by gas chromatography in urine collected for 24 hours after occluded dermal exposure of rats to a hydraulic fluid containing 99.9% cyclotriphosphazene (Kinkead and Bashe 1987).

Urinary excretion of radioactivity has been observed in cats (Nomeir and Abou-Donia 1986) and a dog (Hodge and Sterner 1943) after dermal exposure to radiolabeled TOCP, thereby suggesting that this route of excretion is important following dermal exposure. In cats, cumulative excretion of radioactivity, within 10 days of dermal exposure to [phenyl-^{14}C]TOCP, reached 28% and 20% of the administered dose (50 mg/kg) via the urinary and fecal routes, respectively (Nomeir and Abou-Donia 1986). The importance of biliary excretion was demonstrated in cats by the observation that the peak concentration of radioactivity in bile was much higher than peak concentrations for any other analyzed tissue or body fluid (see Section 2.3.2.3.). Interpretation of the cat data should be addressed with caution, because a portion of the dose was probably ingested during grooming. Peak rates of urinary excretion of radioactivity (equivalent to 202 pg TOCP/hour) were measured for a dog, 12 hours after initiation of a 25.5-hour exposure of a 15x20 cm area of skin to 2.094 g TOCP labeled with radioactive phosphorus (Hodge and Sterner 1943). Radioactivity in urine collected during exposure (the dog was sacrificed immediately following exposure) accounted for 0.14% of the applied dose. Fecal or biliary excretion was not examined.

Urinary excretion of radioactivity after a dermal dose of [^{14}C]tributyl phosphate was 29944% of the applied dose in rats (Gatz 1992b). A large proportion of the dose (24-43%) was recovered in the sitewash at the end of the exposure.

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Polyalphaolefin Hydraulic Fluids. No studies were located regarding excretion in humans or animals after dermal exposure to polyalphaolefin hydraulic fluids or major components.

2.3.4.4 Other Routes of Exposure

Mineral Oil Hydraulic Fluids. No studies were located regarding excretion in humans after exposure by other routes to mineral oil hydraulic fluids.

Within 8 days of an intraperitoneal dose of 0.66 mL/kg tritiated mineral oil to rats, 11% of administered radioactivity was excreted in the feces, predominately in the form of mineral oil (95%) (Ebert et al. 1966). Urine during the same time frame after intraperitoneal administration contained about 8% of the administered radioactivity, but in chemical forms other than mineral oil. The detection of radioactivity in the feces after intraperitoneal administration suggests that significant biliary excretion of absorbed mineral oil can occur.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding excretion in humans after exposure by other routes to organophosphate ester hydraulic fluids.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding excretion in humans or animals after exposure by other routes to polyalphaolefin hydraulic fluids.

2.4 MECHANISMS OF ACTION

Mineral Oil Hydraulic Fluids. The mechanism whereby mineral oil hydraulic fluids may enter the blood from the lungs, skin or gastrointestinal tract is not known. In general, mineral oils and other petroleumderived materials are expected to be absorbed only to a limited extent by the lungs, skin, and the gastrointestinal tract (IARC 1984; Klein and Simon 1986), but data monitoring mineral oil hydraulic fluid components in the blood of animals or humans after exposure were not located.

Data regarding the toxicity of mineral oil hydraulic fluids have not identified definitively specific end points or target organs. However, lipoid pneumonia, lung hemorrhaging, and subsequent death occurred in a 14-month-old boy who ingested 5-10 cc of automobile transmission fluid, thereby indicating that significant aspiration of ingested mineral oil hydraulic fluid can occur (Perrot and Palmer 1992). Clinical experience

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with hydrocarbon poisoning in children indicates that aspiration of ingested petroleum-derived products with subsequent pulmonary edema and hemorrhaging is common (Klein and Simon 1986). The molecular mechanism by which respiratory injury occurs is not known, but interaction of hydrocarbons in mineral oil with pulmonary surfactants has been proposed (Perrot and Palmer 1992).

Organophosphate Ester Hydraulic Fluids. Information regarding the extent of absorption of organophosphate ester hydraulic fluids by the skin, lungs and gastrointestinal tract is very limited and the mechanism by which the organophosphate components of the fluids may enter the blood is unknown.

The most clearly identified toxicological hazard associated with exposure to organophosphate ester hydraulic fluids involves the nervous system. Acute exposures to certain organophosphorus compounds, including certain organophosphate ester hydraulic fluids and organophosphorus insecticides, produce at least one of two types of neurological effects: acetylcholinesterase inhibition resulting in a host of rapidly appearing cholinergic symptoms and a slowly developing axonal degeneration and demyelination in central and peripheral nerve tissues resulting in neuropathy. The delayed neuropathy has been termed organophosphate induced delayed neuropathy (OPIDN).

Organophosphorus cholinesterase inhibitors bind to nervous tissue acetylcholinesterase, thereby inhibiting the catalytic breakdown of the neurotransmitter, acetylcholine (Ecobichon 1991; Murphy 1986). The accumulation of acetylcholine at the nerve endings leads to a continual stimulation of electrical activity along the nerves. Signs of cholinergic toxicity associated with stimulation of muscarinic receptors in smooth muscles, the heart, and exocrine glands include bronchoconstriction and increased bronchial secretions, increased salivation, urination, diarrhea, and bradycardia. Signs associated with stimulation of nicotinic receptors in motor nerve junctions to skeletal muscles and autonomic ganglia include muscle weakness, tremors, muscle fasciculation, tachycardia, and hypertension. Signs associated with acetylcholine accumulation in the central nervous system include restlessness, ataxia, mental confusion, convulsion, and coma (see Table 2-10).

Organophosphorus esters are known to react with a serine hydroxyl group in the active site of the acetylcholinesterase protein (Ecobichon 1991; Murphy 1986). Some organophosphorus esters (e.g., diisopropyl fluorophosphate, [DFP]) bind irreversibly, while others bind in a slowly reversible fashion, thereby leading to a slow reactivation (dephosphorylation) of the enzyme. A process known as “aging” has also been described in which reversibly bound compounds are changed with time to moieties that are essentially irreversibly

Table 2-10. Symptoms and Sites of Acetylcholinesterase Inhibition by Organophosphate Esters

System	Receptor type	Organ	Action	Manifestation
Parasympathetic	Muscarinic	Eye		
		Iris muscle	Contraction	Miosis
		Ciliary muscle	Contraction	Blurred vision
		Glands		
		Lacrimal	Secretion	Tearing
		Salivary	Secretion	Salivation
		Respiratory	Secretion	Bronchorrhea, rhinitis, pulmonary edema
		Gastrointestinal	Secretion	Nausea, vomiting, diarrhea
		Sweat	Secretion	Perspiration
Sympathetic (sympatholytic)		Heart		
		Sinus node	Slowing	Bradycardia
		Atrioventricular (AV node)	Increased refractory period	Dysrhythmias, conduction block
		Smooth muscle		
		Bronchial	Contraction	Bronchoconstriction
		Gastrointestinal wall	Contraction	Vomiting, cramps, diarrhea
		Sphincter	Relaxation	Fecal incontinence
		Bladder		
		Fundus	Contraction	Urination
		Sphincter	Relaxation	Urinary incontinence
Neuromuscular	Nicotinic	Skeletal	Excitation	Fasciculations, cramps, followed by weakness, loss of reflexes, paralysis
		Heart	Excitation	Tachycardia
Central nervous		Brain/brainstem	Excitation (early)	Headache, malaise, dizziness, confusion, manic or bizarre behavior
			Depression (late)	Depression, then loss of consciousness, respiratory depression, diaphragm paralysis

Source: ATSDR 1993c

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bound to the enzyme. Dephosphorylation of reversibly inactivated acetylcholinesterase can be accelerated by certain chemicals, the best known of which is 2-pyridine aldoxime methiodide (pralidoxime). However, 2-pyridine aldoxime methiodide does not dephosphorylate the "aged" phosphorylated enzyme. Thus, to be effective, 2-pyridine aldoxime methiodide must be administered before aging occurs (within 12-48 hours).

Acute exposure to certain organophosphate esters produces a slowly developing neuropathy in humans, OPIDN, that is functionally characterized by initial weakness and subsequent ataxia and paralysis in the lower limbs (8-14 days or longer, following exposure) (Ecobichon 1991; Johnson 1975; Murphy 1986). In severe cases, paralysis may also affect the upper limbs. Recovery is usually slow and is not always complete. Tri-*ortho*-cresyl phosphate (TOCP), an isomer found in tricresyl phosphate, was the first organophosphate ester linked to OPIDN, being responsible for an epidemic of paralysis in the southeastern United States that led to the name "ginger jake paralysis" (Smith 1930) (see Section 2.4). Current manufacturing processes for organophosphate ester hydraulic fluids are designed to minimize production of this isomer, although it is possible that fluids disposed of in the past may be contaminated.

Studies with TOCP have indicated that the delayed neurotoxic responses observed in the adult hen and the cat closely resemble the responses observed in humans and that other species (including the rat, rabbit, and mouse) are relatively insensitive to the delayed neurotoxicity of TOCP (Baron 1981). Other species that are sensitive to OPIDN include dogs, calves, sheep, and nonhuman primates (Baron 1981). Light- and electronmicroscopic studies with cats exposed to TOCP (Cavanagh and Patangia 1965) or di-isopropylfluorophosphate (another agent that produces OPIDN [Bouldin and Cavanagh 1979a, 1979b]) have associated the clinical signs of delayed paralysis with degeneration of the distal ends of the longest and largest axonal fibers. Although acute exposure to TOCP does not produce clinical signs of delayed neuropathy in the rat, it produces acetylcholinesterase inhibition, spinal cord histological damage, and inhibition of brain or spinal cord neurotoxic esterase (see next paragraph) in this insensitive species (Inui et al. 1993; Padilla and Veronesi 1995). Several hypotheses have been proposed to explain species differences in susceptibility to OPIDN including species differences in gastrointestinal absorption (Baron 198 l), in kinetics of tissue clearance (Abou-Donia 1990a, 1990b; Suwita and Abou-Donia 1990), and in unspecified neuroanatomical features (Baron 1981).

The mechanism of OPIDN is poorly understood, but, since all organophosphate esters that produce OPIDN are either direct cholinesterase inhibitors or are metabolically converted to cholinesterase inhibitors, inhibition of an esterase of some kind has generally been thought to be involved (Baron 1981). Certain

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organophosphate esters, including TOCP, are known to require bioactivation before they induce OPIDN (Casida et al. 1961; Eto et al. 1962, 1967; Johnson 1975) (see Section 2.3.3). However, acetylcholinesterase inhibition in nervous tissue is not thought to be primarily involved in OPIDN, because a survey of a wide variety of organophosphate esters showed that not all organophosphate esters that inhibit acetylcholinesterase produce delayed neuropathy (Johnson 1975,1982,1990). The same study, however, found an association between inhibition of the esterase activity of a specific protein, termed "neurotoxic esterase" or "neuropathy target esterase" (NTE), and the development of delayed neuropathy (Johnson, 1982, 1990). Inhibition of brain NTE in animals (by approximately 70-80%) has been proposed as a screening tool or monitor to evaluate the potential of organophosphorus compounds to induce OPIDN (Ecobichon 1991; Johnson, 1982). Inhibition of lymphocytic NTE and inhibition of platelet NTE in humans have been proposed as surrogate markers for brain NTE (Lotti et al. 1984; Maroni and Bleeker 1986). When chickens were exposed to 3 organophosphorus esters, there was good correlation between lymphocyte and brain NTE for only 24 hours; after that lymphocyte NTE was not consistent with OPIDN or brain NTE (Schwab and Richardson 1986). Brain NTE inhibition appears to be a reasonable predictor of OPIDN. The physiological and/or molecular sequence of events involved in the development of OPIDN are not yet defined (Ecobichon 1991; Johnson 1990).

Two types of OPIDN have been described in animals (Abou-Donia and Lapadula 1990). Type I is produced by compounds with a pentavalent phosphorus (like TOCP), and Type II is produced by compounds with a trivalent phosphorus. Characteristics used to differentiate between the types of OPIDN include species selectivity, age sensitivity, length of latent period, and morphology of neuropathologic lesions. Thus, at doses that did not produce death due to acetylcholinesterase inhibition, TOCP (a Type I compound) produced lesions in the spinal cord of rats without producing ataxia. In contrast, triphenyl phosphite (a Type II compound) produced delayed (1 week) ataxia in the rat and a distribution of spinal cord lesions distinct from those produced by TOCP (Abou-Donia and Lapadula 1990).

Conclusions drawn from the review of a large number of organophosphate esters (Johnson 1975) indicate that potency for OPIDN depends on the following factors: 1) esters having one or more rings substituted in the *ortho* position are neurotoxic provided that the *ortho*-alkyl group has at least one hydrogen on the alpha carbon atom; 2) further substitution in the ring containing the *ortho*-substituent greatly reduces neurotoxicity; 3) neurotoxicity is higher in isomers having only one *ortho*-substituent; 4) neurotoxicity decreases as the substituent on the *ortho* position becomes larger and more branched; 5) esters having no *ortho*-substituents are not neurotoxic. OPIDN has not been associated with trialkyl phosphates.

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Tricresyl phosphate (a complex mixture containing tri-*o*, tri-m-, and tri-*para*-cresyl phosphate that is used in certain hydraulic fluids) and TOCP are demonstrated testicular toxicants in rodents (Carlton et al. 1987; Somkuti et al. 1987a, 1987b). Tricresyl phosphate also has been shown to impair *in vivo* fertility in rats and mice (Carlton et al. 1987; Chapin et al. 1988a). In addition, tricresyl phosphate-treated female rats displayed vacuolar cytoplasmic alteration of ovarian interstitial cells (Carlton et al. 1987; NTP 1994). Reproductive effects have also been seen after oral exposure to butylated triphenyl phosphate (Latendresse et al. 1994b).

The mechanism of male reproductive toxicity, but not female reproductive toxicity, has received some research attention. The mechanism by which these substances affect the male reproductive system is not completely understood, but evidence indicates that the production of the testicular effects may involve bioactivation of TOCP to saligenin cyclic-*ortho*-tolyl phosphate in testicular Leydig cells (Chapin et al. 1990, 1991) and the inhibition of esterases (nonspecific esterase, also known as butyrylcholinesterase or NSE, and neurotoxic esterase) by saligenin cyclic-*ortho*-tolyl phosphate in testicular Sertoli cells (Chapin et al. 1991; Somkuti et al. 1987a, 1991). Although inhibition of esterases in testicular cells has been associated with the occurrence of testicular effects including increased frequency of sperm with abnormal morphology, decreased sperm motility, and decreased epididymal sperm density, mechanistic details concerning the specific functions of these esterases currently are unknown.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding the absorption of polyalphaolefin hydraulic fluids following oral, inhalation, or dermal exposure of animals or humans. The mechanism whereby these materials may enter the blood stream is not known.

Acute inhalation exposure to aerosols of certain polyalphaolefin hydraulic fluids produced death in rats associated with respiratory tract irritation, while aerosols of other polyalphaolefin hydraulic fluids produced no apparent respiratory tract irritation or deaths (MacEwen and Vemot 1983; Kinkead et al. 1987b, 1992b). The mechanism by which certain polyalphaolefin fluids may produce respiratory tract irritation is not understood.

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2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

This profile covers three major classes of hydraulic fluids: mineral oil, organophosphate ester, and polyalphaolefin. Information on another phosphorus-containing hydraulic fluid, cyclotriphosphazene, is discussed with the organophosphate esters for convenience. The chemical identity and concentration of hydraulic fluid components may often be proprietary information. This profile primarily focuses on the toxicological properties of hydraulic fluids themselves (identified by commercial name when possible), rather than on the properties of known major components. This focus was taken because it is possible that the toxicity of any particular fluid is influenced by non-additive interactions among the components, as well as by the presence of unknown, but potentially toxic, compounds. The profile also discusses toxicological properties of several major organophosphate ester components of hydraulic fluids because components of a hydraulic fluid contaminating a waste site may be known without having toxicological data for the complete fluid.

Mineral Oil Hydraulic Fluids. There is limited information on the toxicity of mineral oil hydraulic fluids in humans and animals. Death, respiratory effects, gastrointestinal effects, and neurotoxicity have been reported in humans. Severe respiratory effects and mild gastrointestinal effects were observed in a small child who accidentally ingested a lethal dose of automotive transmission fluid (Perrot and Palmer 1992). Peripheral neuropathy was observed in a worker heavily exposed to mineral oil hydraulic fluids by dermal contact (Jarvholm et al. 1986), although the toxicity in this case was attributed to an organophosphate ester additive (isopropyl triphenyl phosphate, 0.5%). The lack of corroborative case reports or epidemiology data make it difficult to extrapolate these data to populations living at or near hazardous waste sites. A series of acute animal inhalation, oral, and dermal exposure studies tested the toxicity of five different mineral oil hydraulic fluids (Kinkead et al. 1985, 1987a, 1989). No deaths, skin sensitization, neurotoxicity, or changes in body weight gain were observed. Following acute ocular exposure to four of the fluids, mild eye irritation was observed; the fifth fluid was not an ocular irritant but did cause moderate skin irritation. Dermal and ocular irritation may occur in humans heavily exposed to these same mineral oil hydraulic fluids. Reproductive and developmental end points have not been examined in animal studies. The most sensitive targets of toxicity of mineral oil hydraulic fluids cannot be identified from these data primarily because of the small number of end points that have been examined. Based on data on the laxative properties of mineral oil, it is likely that the gastrointestinal tract will be affected following oral exposure to mineral oil hydraulic fluid.

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Additionally, there are data which suggest untreated distillates of petroleum and mildly solvent-refined or mildly hydrotreated mineral oils are carcinogenic (IARC 1984). However, highly refined mineral oils do not appear to be carcinogenic. The available data for mineral oils as a class are not adequate to predict whether a particular mineral oil hydraulic fluid will be carcinogenic because of the dependence of carcinogenic activity upon quality of the oil, presence of additives, and potentially, the conditions of use (JARC 1984). Mineral oil hydraulic fluids often contain organophosphate ester additives which may be relevant to assessment of toxicity.

Organophosphate Ester Hydraulic Fluids. A number of studies have been conducted on organophosphate ester hydraulic fluids because of the well known neurotoxic effects caused by organophosphorus insecticides, organophosphorus nerve gases, and tri-*ortho*-cresyl phosphate (TOCP). The following manifestations of acute exposure to organophosphorus compounds have been described:

1. cholinergic symptoms associated with acetylcholinesterase inhibition that develop within 4-12 hours of exposure (see Table 2- 10);

2. "intermediate syndrome," a paralysis of limb muscles and respiratory muscles developing within 24-96 hours after the subsidence of cholinergic symptoms; and

3. "organophosphorus-induced delayed neuropathy" (OPJDN), typically a paralytic condition of the legs, hands, or forearms developing within 7 or 14 days of first exposure (Ecobichon 1991).

Because the "intermediate syndrome" has not been described for animals or humans exposed to hydraulic fluids, this syndrome is not discussed further in this profile.

Some organophosphorus compounds are potent inhibitors of acetylcholinesterase, but do not produce OPIDN; while others display both activities. The chemical structure of organophosphate esters is linked to OPIDN; *ortho* substitution has been associated with neurotoxicity (Johnson 1975). Tri-*ortho*-cresyl phosphate (TOCP), an isomer of tricresyl phosphate, is a well-known example of an organophosphorus compound that induces OPJDN. Current manufacturing processes for tricresyl phosphate are designed to minimize production of this isomer. Contamination of an alcoholic extract of ginger (ginger jake) with TOCP in the southeastern United States produced an epidemic of neuropathies in the 1930s the symptoms of which became known as "ginger jake paralysis" (Smith et al. 1930). No such widespread exposure and outbreak of

neuropathies in humans has been reported for organophosphate ester hydraulic fluids, but controlled animal studies have indicated that neurological effects are the most sensitive toxicological end points for certain organophosphate hydraulic fluids.

Polyalphaolefin Hydraulic Fluids. No information on the toxicity of polyalphaolefin hydraulic fluids to humans was located. Acute animal inhalation, oral, and dermal exposure studies (Kinkead et al. 1985, 1987a, 1992b; MacEwen and Vemot 1983) have examined a limited number of end points. The only end points examined in these studies were death, body weight gain, dermal and ocular irritation, and clinical signs of toxicity. Death, evidence of severe respiratory irritation, and lethargy were observed following inhalation exposure to relatively high concentrations of certain polyalphaolefin hydraulic fluids. Human exposure to high concentrations of these fluids may result in similar effects. No changes in body weight gain or evidence of neurotoxicity were observed following oral exposure. Following dermal exposure, mild eye and skin irritation, as well as skin sensitization were observed for some of the polyalphaolefin hydraulic fluids, and lethargy was observed for all of the polyalphaolefin hydraulic fluids. It is not known whether human exposure to relatively high dermal doses of polyalphaolefin hydraulic fluids will also result in lethargy.
Reproductive and developmental end points have not been examined. The animal data are not sufficient to identify the most sensitive target(s) of toxicity of polyalphaolefin hydraulic fluids because only a limited number of end points have been examined.

Minimal Risk Levels for Hydraulic Fluids.

Rational assessment of the health hazard presented by hydraulic fluid(s) contaminating an environmental medium is not possible without knowing the identity of the contaminating fluid(s) and/or knowing something about the fluids chemical composition. Even if the identity of a contaminating fluid is known and there are sufficient toxicological data for the fluid to derive a Minimal Risk Level (MRL), any resultant hazard assessment would contain an inherent uncertainty because of compositional changes between production batches. Such changes are expected due to different starting materials and production practices (especially for fluids containing processed “natural materials” like mineral oil) and due to unreported changes in production formulation (e.g., change of additives) (see Chapters 3 and 5). Adding to the uncertainty is the possibility that processes in the environment (e.g., physical and biological transformations) may change the composition of the contaminating fluid from that used in toxicological testing.

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Mineral Oil Hydraulic Fluids

Inhalation MRLs.

No inhalation MRLs were derived.

Available data are restricted to acute lethality studies in rats exposed to four water-in-oil emulsion hydraulic fluids or a mineral oil hydraulic fluid for 4-6 hours. No deaths or body weight alterations occurred at exposure concentrations ranging from 180 to 2 10 mg/m^3 for the water-in-oil fluids and 1,130 mg/m^3 for the mineral oil fluid. The data are inadequate for acute inhalation MRL derivation. No data regarding intermediate or chronic inhalation exposure to mineral oil hydraulic fluids were located.

Oral MRLs.

No oral MRLs were derived.

The available data did not adequately identify target organs or effects. In acute lethality studies in rats gavaged with 5,000 mg/kg doses of the water-in-oil emulsion hydraulic fluids or mineral oil hydraulic fluids, no deaths or body weight changes occurred. One of these fluids was tested for neurotoxicity in chickens without effects.

Organophosphate Ester Hydraulic Fluids

Inhalation MRLs

No inhalation MRLs were derived.

No NOAELs or LOAELs were identified for toxic effects in humans after inhalation exposure to organophosphate ester hydraulic fluids. Reliable NOAELs and LOAELs for acute inhalation exposure are restricted to 4-hour NOAELs for systemic effects in rats exposed to Fyrquel220 or Durad MP280 and 4-hour LOAELs for mild lethargy in rats exposed to Durad MP280 and Fyrquel 220 (Gaworski et al. 1986). The study identifying these NOAEL and LOAEL values did not measure cholinesterase inhibition, did not allow sufficient follow-up time for the development of delayed neurotoxic effects, and used a species that is

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relatively insensitive to OPIDN. An acute inhalation MRL was not derived for organophosphate ester hydraulic fluids as a class due to the inadequacy of the available data to assess the neurotoxicity of Fyrquel 220 and Durad MP280 and the lack of any acute inhalation data for other organophosphate ester hydraulic fluids.

There are insufficient data to derive hydraulic fluid-specific acute-duration inhalation MRLs. No systemic effects were observed in rats exposed to 6,350 mg/m^3 of Durad MP280 for 4 hours (Gaworski et al. 1986). Mild lethargy was observed 1-3 hours post-exposure to 6,190 and 6,350 mg/m^3. Longer-term inhalation exposure to Durad MP280 resulted in testicular atrophy in rats (MacEwen and Vemot 1983). Reproductive end points have not been examined following acute inhalation exposure. In rats exposed to Fyrquel 220, no systemic effects were observed following exposure to 6,3 10 mg/m^3 and mild lethargy was observed at ≥5,790 mg/m^3 (Gaworski et al. 1986; Kinkead et al. 1992a). The short duration of the study (single 4-hour exposure), the lack of testing in a species sensitive to the neurotoxic effects, and the lack of reproductive testing (especially for Durad MP280) precludes deriving acute-duration inhalation MRLs for Durad MP280 and Fyrquel 220.

Reliable intermediate-duration inhalation NOAELs and LOAELs were located for systemic effects in rats and rabbits exposed to several organophosphate ester hydraulic fluids (Durad MP280, Fyrquel 220, Skydrol 500B-4, or Cellulube 220) and cyclotriphosphazene. Neurological effects were observed in rats, rabbits, dogs, hamsters, monkeys, and hens exposed to Durad MP280, Fyrquel 220, Skydrol 500B-4, Cellulube 220, or triaryl phosphate. In addition, reproductive effects (histological alteration of reproductive organs) were observed in rats, rabbits, and hamsters exposed to cyclotriphosphazene, Durad MP280, or Fyrquel 220. Based on the lowest LOAEL, the most sensitive end point appears to be the neurological effects. The NOAELs for neurological effects ranged from 4.4 to 260 mg/m^3 and the range of serious LOAELs was 23 to 2,000 mg/m^3. Not all of the organophosphate ester hydraulic fluids tested had the same targets. For example, head droop and generalized weakness or lethargy were observed in rabbits exposed to 2,000 mg/m^3 (lowest concentration tested) of Cellulube 220 4 hours/day, 4-5 days/week for 11 or 22 days (Carpenter et al. 1959) and 101 mg/m^3 of Durad MP280 continuously for 90 days (MacEwen and Vemot 1983). No neurological effects were observed in rabbits continuously exposed to 100 mg/m^3 of Fyrquel 220 for 90 days (MacEwen and Vemot 1983). Testicular atrophy was observed in rats continuously exposed to 101 mg/m^3 Durad MP280, but not in rats continuously exposed to Fyrquel 220 for 90 days (MacEwen and Vemot 1983), rats exposed for 13 weeks (6 hours/day, 5 days/week) to Skydrol 500B-4 (Healy et al. 1992; Monsanto 1987a, 1987b, 1989), or rats exposed to 990 mg/m^{3}of cyclotriphosphazene for 21 days (6 hours/day,

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5 days/week) (Kinkead et al. 1989b, 1990). No intermediate inhalation MRL was derived for organophosphate ester hydraulic fluids as a class because of the uncertainty that derivation of a MRL based on data for a single fluid with the lowest identified threshold would be representative for other fluids in the class.

The available inhalation data for Durad MP280, Fyrquel 220, Cellulube 220, Skydrol 500B-4, and cyclotriphosphazene (reviewed in the next paragraph) are inadequate to derive intermediate-duration MRLs for these individual fluids, principally because the studies were conducted in species (rats or rabbits) that are generally considered to be insensitive to the delayed neurotoxicity of acute exposure to organophosphate esters. Cats, dogs, or nonhuman primates more accurately model the human expression of OPIDN than rats and rabbits, and studies in these species would provide a better basis for MRL derivation.

Following a 90-day continuous exposure to 101 mg/m^3 of Durad MP280, leukocytosis, kyphosis, and testicular atrophy were observed in rats and 100% mortality, cachexia, head droop, anorexia, and lethargy were observed in rabbits. No effects were observed in either species at 10.3 mg/m^3 Durad MP280 (MacEwen and Vemot 1983). Continuous exposure to 100 mg/m^3 of Fyrquel220 for 90 days resulted in kyphosis in rats (MacEwen and Vemot 1983); the NOAEL for this effect was 10.1 mg/m^3. No adverse effects were observed in rabbits exposed to 100 mg/m^3 Fyrquel 220 continuously for 90 days (MacEwen and Vemot 1983). At the lowest tested concentration of Cellulube 220 (2,000 mg/m^3, 4 hours/day, 4-5 days/week for 11 or 22 days), severe dyspnea, head droop, and generalized weakness were observed in rabbits (Carpenter et al. 1959). No adverse effects were observed in rats exposed to 990 mg/m^3 of cyclotriphosphazene (6 hour/day, 5 days/week) for 21 days (Kinkead et al. 1989b, 1990). Exposure of rats to Skydrol500B-4 for 13 weeks (6 hours/day, 5 days/week) resulted in nasal discharge at 100 mg/m^3, decreased erythrocyte, hemoglobin, and hematocrit levels at 300 mg/m^3, and decrease in plasma cholinesterase activity at 300 mg/m^3 (Healy et al. 1992; Monsanto 1987a, 1987b, 1989). Mild hepatocellular vacuolization and excessive salivation, a sign of cholinergic neurotoxicity, were also observed in these studies at 300 mg/m^3. The lowest LOAEL is 5.3 mg/m^3 Skydrol 500B-4 for nasal effects. No chronic exposure data were located.

2. HEALTH EFFECTS

Oral MRLS

No oral MRLs were derived.

No data are available regarding systemic or neurological effects in humans after oral exposure to organophosphate ester hydraulic fluids. The acute oral data base consists of a number of studies examining limited end points. Effects associated with cholinesterase inhibition (e.g., diarrhea) and OPIDN have been observed. Extensive testing of organophosphate ester hydraulic fluids in chickens (this species is generally thought of as one of the most sensitive to the neurotoxicity of organophosphorus compounds and a valid model species for identifying neurotoxic potential in humans) has demonstrated that there is a wide diversity in the ability of organophosphate ester hydraulic fluids to produce neurological effects. Some fluids produced no signs of neurological effects in chickens after administration of substantial doses (e.g., Pydraul29ELT, Pydraul50E, and Pydraul90E), other fluids produced only subtle neurological effects (e.g., Skydrol500B-4, Skydrol LD-4, and Reofos 65), and a few produced frank neurological effects (OPIDN) at comparatively low doses (e.g., Cellulube 220 and Fyrquel 150). A comparison of the relative toxicity of the different organophosphate ester hydraulic fluids is difficult because many of the studies only tested one dose level or a NOAEL was not identified. For hydraulic fluids causing cholinesterase inhibition effects, the LOAELs ranged from 120 mg/kg/day in rabbits for Cellulube 220 (Carpenter et al. 1959) to 5,750 mg/kg in rats exposed to Fyrquel 220 (Gaworski et al. 1986; Kinkead et al. 1992a). NOAELs for this effect were not reported. Inhibition of brain neurotoxic esterase and butyrylcholinesterase were observed in chickens exposed to approximately 2,600 mg/kg Skydrol500B-4 (Monsanto 1987d) or Skydrol LD-4 (Monsanto 1987c) and 114 mg/kg Fyrquel EHC (Stauffer Chemical Co. 1981). The range of LOAELs for OPIDN was 60 mg/kg/day for chickens exposed to Cellulube 220 for 5 days (Carpenter et al. 1959) to 11,350 mg/kg in chickens exposed once to Fyrquel EHC (Stauffer Chemical Co. 1980).

Derivation of an acute-duration oral MRL for organophosphate ester hydraulic fluids as a class based on the lowest identified reliable LOAEL for neurological effects in chickens (60 mg/kg/day Cellulube 220 for leg and wing weakness) (Carpenter et al. 1959) is not recommended for two reasons. First, the LOAEL is a serious LOAEL (no NOAEL was identified in the study) and MRLs are not derived from serious LOAELs. Second, the wide diversity in the apparent neurotoxicities among members of the class indicates that derivation of an MRL based on data for a single fluid may not be representative for the class. Acute-duration oral MRLs for individual organophosphate ester hydraulic fluids have not been proposed. In addition,

although chickens have been identified as a good species for qualitatively identifying the neurotoxicity of organophosphate esters, the extrapolation of chicken doses to human doses is uncertain.

Reliable NOAELs and LOAELs for intermediate oral exposure are restricted to a 90-day NOAEL of 50 mg/kg/day for systemic toxicity in rats (a species that is not sensitive to the neuropathic effects of organophosphate esters) exposed to Pydraul 90E for 90 days and NOAELs and LOAELs for delayed neuropathy in chickens exposed to Durad 110. In chickens exposed to Durad 110 for 28 days, a NOAEL of 444 mg/kg/day and LOAEL of 1,333 mg/kg/day were identified (FMC 1986); when the duration was increased to 90 days, the NOAEL was 20 mg/kg/day and the LOAEL was 90 mg/kg/day (FMC 1986). These data are inadequate for derivation of an intermediate oral MRL for organophosphate ester hydraulic fluids. As discussed under the acute-duration oral MRL section, there is uncertainty regarding extrapolation of chicken doses to human doses.

No data were located regarding chronic oral exposure to organophosphate ester hydraulic fluids

Toxicity data are available for several organophosphate ester components of hydraulic fluids, in particular tricresyl phosphate (NTP 1994). However, these components are always present in products as mixtures with other chemicals. Since insufficient information exists to assess the effect on toxicity of interactions among these mixtures, MRLs for the components were not derived.

Polyalphaolefin Hydraulic Fluids

Inhalation MRLs

No inhalation MRLs were derived.

No data were located regarding toxic effects in humans following inhalation exposure to polyalphaolefin hydraulic fluids. Three of nine tested polyalphaolefin hydraulic fluids were lethal in rats at 4-hour aerosol concentrations ranging from <5,330 to <10,720 mg/m^3. LC_{50} values for the three lethal fluids in females ranged from 1,390 to 1,670 mg/m^3. Deaths were associated with respiratory irritation. The data are inadequate for acute inhalation MRL derivation. No intermediate or chronic inhalation MRLs for polyalphaolefin hydraulic fluids were derived due to the lack of data.

2. HEALTH EFFECTS

Oral MRLS

No oral MRLs were derived.

No data were located regarding toxic effects in humans following oral exposure to polyalphaolefin hydraulic fluids. No deaths or body weight changes occurred in rats in a series of acute lethality studies with nine polyalphaolefin hydraulic fluids at doses ranging from 4,250 to 5,000 mg/kg. One of these fluids was also tested for neurotoxicity in chickens, and did not produce effects at 4,250 mg/kg. The available data have not identified a target organ or effect for these fluids. The data are inadequate for MRL derivation. No intermediate or chronic oral MRLs for polyalphaolefin hydraulic fluids were derived due to the lack of data.

Death.

Mineral Oil Hydraulic Fluids. Only one report was located regarding death in humans following exposure to mineral oil hydraulic fluids. A 14-month-old boy ingested 5-10 cc of a mineral oil hydraulic fluid and died 4 weeks later after developing pneumonia (Perrot and Palmer 1992). Postmortem analysis revealed edema, hemorrhages, and lipoid/oil droplets in the lungs. The attending physicians believed that the development of lipoid pneumonia with marked interstitial pneumonitis eventually led to death.

Acute lethality studies in animals exposed by inhalation, ingestion, or dermal contact to several mineral oil hydraulic fluids indicate that mineral oil fluids are not potent toxicants. Mineral oil hydraulic fluids produced no deaths in rats after 4-hour exposures to aerosol concentrations of 11 0-2 10 mg/m^3or gavage administration of single doses $\leq$5,000 mg/kg (Kinkead et al. 1987a, 1988). Rabbits, likewise, did not die after single 24-hour exposures to occluded dermal doses of several mineral oil hydraulic fluids $\leq$2,000 mg/kg (Kinkead et al. 1985,1987a, 1988).

Organophosphate Ester Hydraulic Fluids. No reports were located regarding deaths in humans following exposure to organophosphate ester hydraulic fluids. As reviewed in Section 2.2, acute to intermediate exposures to certain organophosphate ester hydraulic fluids, but not all tested fluids in this class, have produced lethal neurotoxic effects in animals through effects associated either with cholinesterase inhibition or delayed development of axonal degeneration and demyelination. Evidence is available that humans are susceptible to both types of neurotoxicity by organophosphorus compounds in general (Johnson 1982; Smith

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et al. 1930), indicating that lethal neurotoxic effects may occur in humans at appropriate dosage levels and exposure durations.

Lethal neurotoxicity in animals occurred after inhalation and oral exposure at levels that may be considered high for most environmental media. Lethal neurotoxic effects have not been observed in controlled studies with animals dermally exposed to several organophosphate ester hydraulic fluids at 24-hour dose levels $\leq$ 2,000 mg/kg (Gaworski et al. 1986; Kinkead et al. 1992a), but combined dermal and oral acute exposure of cows to waste from reclamation of an organophosphate hydraulic fluid produced lethal neurotoxic effects (Julian et al. 1976). The lowest lethal aerosol concentrations of organophosphate hydraulic fluids identified in animals after acute to intermediate inhalation exposure were for the U.S. military fluid, triaryl phosphate: 23 mg/m^3 in chickens and 102 mg/m^3 in rabbits exposed continuously for 30-160 days (Siegel et al. 1965). The lowest lethal doses of organophosphate hydraulic fluids identified in animals after acute to intermediate oral exposure were for Cellulube 220 in rabbits given 120 mg/kg/day for 2-14 days (Carpenter et al. 1959) and for Fyrquel 150 in chickens given single doses of 300 mg/kg (Stauffer Chemical Co. 1971). Oral exposure to tricresyl phosphate for up to 2 years had no effect on mortality in rats or mice (NTP 1994).

Polyalphaolefin Hydraulic Fluids. Reports of deaths in humans following exposure to polyalphaolefin hydraulic fluids were not located. Inhalation of several polyalphaolefin hydraulic fluids (N501, MIL-83282-LT, and BSS-174) produced deaths in rats associated with acute respiratory irritation and congestion (4-hour LC_{50} values ranged from 1,390 to 1,670 mg/m^3 for females). Several other polyalphaolefin fluids produced no deaths after 4-hour exposures to 5,350-10,720 mg/m^3(Kinkead et al. 1987b, 1992b; MacEwen and Vernot 1983). None of these fluids produced deaths in animals following single gavage doses <5,000 mg/kg.

Systemic Effects.

Respiratory Effects.

Mineral Oil Hydraulic Fluids. There is a paucity of data on respiratory effects following inhalation, oral, ordermal exposure to mineral oil hydraulic fluids. The only available information for humans comes from a case report of a child ingesting a lethal dose of an automotive transmission fluid, which was most likely amineral oil hydraulic fluid. Lipoid pneumonia with marked fibrosis was observed (Perrot and Palmer 1992). It is likely that some of the fluid was aspirated and that the oil caused irritation of the lung tissue. Lipoidpneumonia is frequently reported among people who chronically use medicated oils via intranasa sprays or

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nose drops (Cannon 1940; Lushbaugh 1950). It is unlikely that individuals living at or near hazardous waste sites contaminated with mineral oil hydraulic fluids would ingest (and subsequently aspirate) or inhale sufficient mineral oil to produce lipoid pneumonia. In the only animal study available, histopathological examination of the lungs from rats exposed to $\leq$ 1.0 mg/m^3 of the water-in-oil emulsion hydraulic fluid Houghto-Safe 5047F for 90 days, 23 hours/day, showed no treatment-related lesions (Kinkead et al. 1991).

Organophosphate Ester Hydraulic Fluids. No studies were located regarding respiratory effects in humans after inhalation, oral, or dermal exposure to organophosphate ester hydraulic fluids. The most commonly reported respiratory effects in animals are dyspnea and rapid respirations. These effects have been observed in rabbits exposed to 2,000 mg/m^3 of airborne Cellulube 220 (Carpenter et al. 1959); in cows and goats exposed to oral doses of 5,000 and 7,700 mg/kg of Cellulube 220, respectively, (Dollahite and Pierce 1969); in cows eating grass contaminated with Fyrquel 150 (Beck et al. 1977); in cows orally exposed to 500 mg/kg (Beck et al. 1977); and in rabbits dermally exposed to Cellulube 220 (Carpenter et al. 1959). It is likely that the respiratory effects observed shortly after exposure were the result of acetylcholinesterase inhibition (see section on neurological effects for more information on cholinesterase inhibition) rather than a direct effect on the respiratory tract. Other respiratory effects include nasal discharge in rats exposed to Skydrol 500B-4 for an intermediate duration (Healy et al. 1992; Monsanto 1987a, 1987b, 1989) and rats orally exposed to Durad 110 for an acute duration (FMC 1990a); bronchopneumonia in rabbits acutely exposed to orally administered Cellulube 220 (Carpenter et al. 1959); and emphysema and intralobular fibrosis in cows eating grass contaminated with Fyrquel 150 (Beck et al. 1977). It is not known whether the respiratory effects observed following oral exposure to organophosphate ester hydraulic fluids were due to aspiration of the hydraulic fluid. Following acute and intermediate inhalation exposure to a number of organophosphate ester hydraulic fluids, including Fyrquel 220, Durad MP280, and cyclotriphosphazene, no evidence of gross and/or histological damage was observed in rats, rabbits, hamsters, dogs, monkeys, and hens (Carpenter et al. 1959; Gaworski et al. 1986; Kinkead et al. 1989a, 1990; MacEwen and Vemot 1983; Siegel et al. 1965). Based on the observations of dyspnea in cows, goats, and rabbits exposed to hydraulic fluids, it is likely that sufficient exposure to organophosphate ester hydraulic fluids that contain acetylcholinesterase inhibitors would result in dyspnea in humans.

Polyalphaolefin Hydraulic Fluids. No information was located on the toxicity of polyalphaolefin hydraulic fluids to the respiratory tract of humans following inhalation, oral, or dermal exposure. Animal data suggest that certain airborne polyalphaolefin hydraulic fluids may be respiratory tract irritants. Bloody nasal discharge, rapid and shallow breathing, lung congestion, and perivascular and peribronchial edema have been

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observed in rats acutely exposed to polyalphaolefin hydraulic fluids (Kinkead et al. 1987b, 1992b; MacEwen and Vemot 1983). No information was located on respiratory effects in animals orally or dermally exposed to polyalphaolefin hydraulic fluids.

Cardiovascular Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding cardiovascular effects in humans after inhalation, oral, or dermal exposure to mineral oil hydraulic fluids. In the only animal study available, histopathological examination of the hearts from rats exposed to ≤1.0 mg/m^3 of the water-in-oil emulsion hydraulic fluid Houghto-Safe 5047F for 90 days, 23 hours/day, showed no treatment-related lesions (Kinkead et al. 1991).

Organophosphate Ester Hydraulic Fluids. No studies regarding cardiovascular effects in humans after inhalation, oral, or dermal exposure to organophosphate ester hydraulic fluids or cyclotriphosphazene were located. Animal data suggest that the cardiovascular system would not be a direct target of organophosphate ester hydraulic fluid toxicity. No gross and/or histological damage was observed in animals intermediately exposed to airborne Fyrquel 220, Durad MP280 (Gaworski et al. 1986; MacEwen and Vemot 1983), Skydrol 500B-4 (Healy et al. 1992; Monsanto 1976a, 1987b, 1989), cyclotriphosphazene (Kinkead et al. 1989a, 1990), or triaryl phosphate hydraulic fluids (Carpenter et al. 1959; Siegel et al. 1965); acute oral doses of triaryl phosphate hydraulic fluids (Carpenter et al. 1959; Kinkead et al. 1989b) or intermediate oral doses of Pydraul 90E (Monsanto 1979); or to intermediate dermal applications of Fyrquel 220 (MacEwen and Vemot 1983), cyclotriphosphazene (Kinkead et al. 1989a, 1990), or Cellulube 220 (Carpenter et al. 1959). Although no direct histological effects on the cardiovascular system have been observed in studies with organophosphate ester hydraulic fluids, organophosphate esters that inhibit acetylcholinesterase can overstimulate muscarinic receptors in the heart resulting in bradycardia or complete heart block (arrest) (Murphy 1986). Tachycardia can also result due to stimulation of sympathetic ganglia to overcome bradycardia due to muscarinic overstimulation (Murphy 1986).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding cardiovascular effects in humans after inhalation, oral, or dermal exposure to polyalphaolefin hydraulic fluids or in animals after inhalation or dermal exposure. The only information available on the cardiovascular effects of polyalphaolefin hydraulic fluids is a histopathology finding that oral exposure to MIL-H-83282 and MIL-H-83282LT for 4 weeks at ≤1,000 mg/kg/day in the rat had no effect on the heart (Mattie et al. 1993).

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Gastrointestinal Effects.

Mineral Oil Hydraulic Fluids. The only information available on gastrointestinal effects in humans or animals exposed to mineral oil hydraulic fluids is from a case report of a child ingesting a lethal dose of automotive transmission fluid, which was probably a mineral oil hydraulic fluid. Subserosal hemorrhages were observed in the small and large intestine and omentum (Perrot and Palmer 1992). Focal gastritis with edema was also noted in rats receiving 1,000 mg/kg/day of MIL-H-5606 (Mattie et al. 1993). Mineral oils (petroleum-derived aliphatic hydrocarbons) are known to have laxative effects, to interfere with absorption of essential fat-soluble substances, and to cause foreign body reactions in the intestinal mucosa (Brunton 1985). These data, however, are not adequate to determine the likelihood of individuals living at or near hazardous waste sites having gastrointestinal effects from exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. Gastric upset and diarrhea have been reported in humans following oral exposure to organophosphate ester hydraulic fluid components (Goldstein et al. 1988; Srivastava 1990). In animals, the most widely reported gastrointestinal effect is diarrhea. Diarrhea (or soft feces) has been observed following oral exposure of rats to Durad MP280 (Gaworski et al. 1986), rabbits to Cellulube 220 (Carpenter et al. 1959; Dollahite and Pierce 1969), hens to Skydrol 500B-4 (Monsanto 1987d) or Skydrol LD-4 (Monsanto 1987c), and cows to Cellulube 220 (Dollahite and Pierce 1969) or Fyrquel 150 (Beck et al. 1977). Diarrhea (or soft feces) has also been observed in rabbits dermally exposed to Fyrquel 220 (Gaworski et al. 1986; MacEwen and Vemot 1983) or Cellulube 220 (Carpenter et al. 1959). The studies that reported diarrhea did not conduct histological examinations of the gastrointestinal tract. However, it is possible that the diarrhea was the result of acetylcholinesterase inhibition (see discussion on neurological effects) rather than direct damage to the gastrointestinal tract. In other studies, gastrointestinal effects have not been observed in rats, rabbits, and hamsters exposed to Fyrquel 220 or Durad MP280 (MacEwen and Vemot 1983) Skydrol 500B-4 (Healy et al. 1992; Monsanto 1987a, 1987b, 1989), cyclotriphosphazene (Kinkead et al. 1989a, 1990), or Cellulube 220 (Carpenter et al. 1959). Because the gastrointestinal effects are possibly the result of acetylcholinesterase inhibition rather than direct damage, it is likely that there will not be route-specific differences. Based on the results of the animal studies, it is likely that humans exposed to sufficient organophosphate ester hydraulic fluids to inhibit acetylcholinesterase will exhibit gastrointestinal effects.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding gastrointestinal effects in humans or animals after inhalation, oral, or dermal exposure to polyalphaolefin hydraulic fluids.

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Hematological Effects.

Mineral Oil Hydraulic Fluids. No information on hematological effects in humans after inhalation, oral, or dermal exposure to mineral oil hydraulic fluids is available. In another animal study, a statistically significant reduction of 16% was reported in the percentage of lymphocytes in whole blood in rats receiving 1,000 mg/kg/day MIL-H-5606 by gavage for 26 days (Mattie et al. 1993).

Organophosphate Ester Hydraulic Fluids. There is limited information on hematological effects following exposure to organophosphate ester hydraulic fluids. In workers dermally exposed to triaryl phosphate hydraulic fluids for an intermediate duration, no changes in the levels of leukocytes were observed (Baldridge et al. 1959). This study is limited because leukocyte levels were the only hematological parameter monitored. No other human studies examining hematological parameters were located. Significant decreases in erythrocyte, hemoglobin, and hematocrit levels were observed in rats exposed to 300 mg/m^3 of Skydrol 500B-4 (Healy et al. 1992; Monsanto 1987a, 1987b, 1989) and leukocytosis was observed in male rats exposed to 101 mg/m^3 Durad MP280 (MacEwen and Vemot 1983); both of these studies were for intermediate durations. A number of intermediate-duration animal studies examined hematological parameters, but no significant effects were found. Hematological examinations were made after inhalation exposure to Durad MP280, Fyrquel 220, and cyclotriphosphazene (Gaworski et al. 1986; Kinkead et al. 1989a, 1990; MacEwen and Vemot 1983); oral exposure to Pydraul90E (Monsanto 1979); and dermal exposure to cyclotriphosphazene (Kinkead et al. 1989c, 1990) and Fyrquel 220 (MacEwen and Vemot 1983). Studies of oral exposures to MIL-H-83306 also have shown decreased hematocrits, erythrocyte numbers, and hemoglobin at levels of 250 mg/kg and 500 mg/kg, respectively (Mattie et al. 1993). A chronic-duration study of oral exposure to tricresyl phosphate for 2 years in rats and mice showed no alteration in hematological parameters (NTP 1994).

Polyalphaolefin Hydraulic Fluids. Studies examining hematological effects in humans or animals following inhalation, oral, or dermal exposure to polyalphaolefin hydraulic fluids are limited to a 4-week study in rats orally exposed to 1,000 mg/kg/day of MIL-H-83282 or MIL-H-83282LT (Mattie'et al. 1993). No effect was seen with MIL-H-83282 but reductions in total and mean cell hemoglobin as well as anemia were seen in rats exposed to MIL-H-83282LT.

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Musculoskeletal Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding musculoskeletal effects in humans or animals after inhalation, oral, or dermal exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No human studies examining musculoskeletal effects following inhalation, oral, or dermal exposure to organophosphate ester hydraulic fluids were located. No musculoskeletal abnormalities were observed in rabbits and hens orally exposed to Cellulube 220 for an acute duration (Carpenter et al. 1959). In rats, kyphosis was observed following intermediate-duration exposure to ≈ 100 mg/m^3 of Durad MP280 or Fyrquel 220 (MacEwen and Vemot 1983). It is not known if this deformity of the spine characterized by extension flexion is the result of damage to musculoskeletal system or a neurological effect. No histological damage to the skeletal muscle was observed following intermediateduration inhalation exposure of rats or dermal exposure of rabbits to cyclotriphosphazene (Kinkead et al. 1989a, 1989~ 1990) or rabbits to Cellulube 220 (Carpenter et al. 1959). There is insufficient information to determine the likelihood of humans having musculoskeletal effects following exposure to organophosphate ester hydraulic fluids.

Polyalphaolefin Hydraulic Fluids. There is limited information on the potential of polyalphaolefin hydraulic fluids to induce musculoskeletal effects. Kyphosis, a deformity of the spine characterized by extension flexion was observed in rats exposed to 880-5,030 mg/m^3 (concentration eliciting response not reported) of a polyalphaolefin hydraulic fluid designated at B85-174 for 4 hours (Kinkead et al. 1987b). It is not known if this effect is related to damage to the musculoskeletal system or to neurological damage. This is the only study that examined musculoskeletal effects. Thus, the likelihood of musculoskeletal effects occurring in humans exposed to polyalphaolefin hydraulic fluids cannot be determined.

Hepatic Effects.

Mineral Oil Hydraulic Fluids. No studies regarding hepatic effects in humans following inhalation, oral, or dermal exposure to mineral oil hydraulic fluids were located. In an animal study, histopathological examination of the livers from rats exposed by inhalation to $\leq$ 1.0 mg/m^3 of the water-in-oil emulsion hydraulic fluid Houghto-Safe 5047F for 90 days, 23 hours/day, showed no treatment-related lesions (Kinkead et al. 1991). Animal data for oral exposure are limited to one study where rats were exposed to MLH-5606

at 1,000 mg/kg/day for 26 days (Mattie et al. 1993). Increases in liver weight and peroxisomal betaoxidation activity were observed.

Organophosphate Ester Hydraulic Fluids. No human exposure studies examining hepatic end points were located. Several hepatic effects have been observed in animals after exposure to organophosphate ester hydraulic fluids. Mild hepatocellular vacuolation and increased liver weight were found in rats exposed to 300 mg/m^3 Skydrol500B-4 (Healy et al. 1992; Monsanto 1987a, 1987b, 1989). Increased smooth endoplasmic reticulum was seen with increased liver weight after oral exposure in rats to MIL-H-83306 at 500 mg/kg/day for 26 days (Mattie et al. 1993). Evidence of adverse histological alterations and/or changes in serum enzymes indicative of liver damage was not observed in other inhalation studies (Carpenter et al. 1959; Healy et al. 1992; Kinkead et al. 1989a, 1990, 1992a; Monsanto 1987a, 1987b, 1989; Siegel et al. 1965), in oral exposure studies (Carpenter et al. 1959; Monsanto 1979), or in dermal exposure studies (Carpenter et al. 1959; Kinkead et al. 1989c, 1990; MacEwen and Vemot 1983). Increased fatty accumulation and decreased hepatocyte vacuolization, along with increased absolute and relative liver weights were observed in rats orally exposed to dibutylated phenyl phosphate for 91 days at 250 mg/kg/day (Healy et al. 1991). Minimal to mild papillary hyperplasia of the gallbladder mucosa was observed in mice orally exposed to tricresyl phosphate at 11 0-230 mg/kg/day for 13 weeks (NTP 1994). In 2-year feeding studies, clear cell foci, fatty change, and ceroid pigmentation were observed in mice but not in rats (NTP 1994).

Polyalphaolefin Hydraulic Fluids. The only information available on hepatic effects of polyalphaolefin hydraulic fluids in humans or animals is a report of increased peroxisomal beta-oxidation and serum alkaline phosphatase after oral exposure in rats to 1,000 mg/kg/day MIL-H-83282 for 26 days (Mattie et al. 1993). Increased peroxisomal beta-oxidation but no increase in serum alkaline phosphatase was observed in rats similarly treated with MIL-H-83282LT.

Renal Effects.

Mineral Oil Hydraulic Fluids. The only information regarding renal effects in humans or animals following inhalation, oral, or dermal exposure to mineral oil hydraulic fluids are two animal studies. Histopathological examination of the kidneys from rats exposed to ≤ 1.0 mg/m^3 of the water-in-oil emulsion hydraulic fluid Houghto-Safe 5047F for 90 days, 23 hours/day, showed no treatment-related lesions (Kinkead et al. 1991). Persistent diuresis, and increased protein and protein/creatinine ratios in the urine were reported in rats orally

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exposed to 1,000 mg/kg/day MIL-H-5606 for 26 days (Mattie et al. 1993). Hyaline droplets were also observed in the proximal tubule on histopathological examination.

Organophosphate Ester Hydraulic Fluids. No human studies examining renal end points were located. No renal effects were observed in rats exposed by inhalation to ≈6,300 mg/m^3 of Durad MP280 or Fyrquel 220 for 4 hours (Gaworski et al. 1986; Kinkead et al. 1992a) or in rabbits exposed orally to 120 mg/kg/day Cellulube 220 for ≤14 days (Carpenter et al. 1959). A minimal to mild accumulation of hyaline droplets was found in the kidneys of male and female rats exposed to ≥240 mg/m^3 of cyclotriphosphazene for 90 days (Kinkead et al. 1989a, 1990). Orally exposed mice showed renal tubule degeneration at 430-730 mg/kg/day tricresyl phosphate over 13 weeks (NTP 1994). Urinary bladder hyperplasia was observed after oral exposure in rats to tributyl phosphate at 55-350 mg/kg (Healy et al. 1991; Laham et al. 1985). In rabbits exposed dermally to ≥2,882 mg/kg/day of Fyrquel 220 for an intermediate duration, significant increases in serum urea nitrogen and creatinine levels were observed (MacEwen and Vernot 1983); this study did not report the results of histological examination of the kidneys. Interpretation of this study is complicated by the fact that one of the rabbits was infected with *Pasturella.* Other intermediate-duration inhalation studies have found no gross or histological damage in the kidneys of rats, rabbits, hamsters, dogs, monkeys, and hens exposed to Durad MP280 (Gaworski et al. 1986; MacEwen and Vernot 1983) Fyrquel 220 (Gaworski et al. 1986; MacEwen and Vernot 1983), Skydrol 500B-4 (Healy et al. 1992; Monsanto 1987a, 1987b, 1989), Cellulube 220 (Carpenter et al. 1959), and a triaryl phosphate hydraulic fluid (Siegel et al. 1965). In addition, no evidence of renal damage was observed following intermediate-duration exposure of rats to oral doses of Pydraul 90E (Monsanto 1979), rabbits to topical cyclotriphosphazene (Kinkead et al. 1989c, 1990), or rabbits to topical Cellulube 220 (Carpenter et al. 1959).

Polyalphpolejin Hydraulic Fluids. The only information on renal effects in humans or animals following inhalation, oral, or dermal exposure to polyalphaolefm hydraulic fluids is a report of increased urinary protein to creatinine ratio of rats orally exposed to MIL-H-83282 at 1,000 mg/kg/day for 4 weeks. Diuresis was noted in rats similarly exposed to MIL-H-83282LT (Mattie et al. 1993).

Endocrine Effects.

Mineral Oil Hydraulic Fluids. No information on endocrine effects in humans or animals following inhalation, oral of dermal exposure to mineral oil hydraulic fluids was located.

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Organophosphate Ester Hydraulic Fluids. No information on endocrine effects in humans following inhalation, oral, or dermal exposure to organophosphate ester hydraulic fluids was located.

There are some equivocal data suggesting that the adrenal gland is a target for organophosphate ester hydraulic fluid toxicity. Nodular hyperplasia was observed in the adrenal cortex of one of two dogs examined following 20 subcutaneous injections of an unspecified amount of Cellulube 220 (Carpenter et al. 1959). No adrenal effects were observed in rats continuously exposed to 100 mg/m^3 Fyrquel 220 or 101 mg/m^3 Durad MP280 for 90 days (MacEwen and Vemot 1983); rats exposed to 300 mg/m^3 Skydrol 500B-4,6 hours/day, 5 days/week for 13 weeks (Healy et al. 1992; Monsanto 1987a, 1987b, 1989); or rabbits inhaling 2,000 mg/m^3 Cellulube 220,4 hours/day, 4-5 days/week for 11 or 22 days (Carpenter et al. 1959). Rabbits receiving repeated dermal exposure (6 hours/day, 5 days/week for 21 days) to 1,000 mg/kg cyclotriphosphazene (Kinkead et al. 1989c, 1990) did not have adrenal effects. In a reproductive toxicity study (Chapin et al. 1988) in which male and female mice were exposed to 62.5 mg/kg of a mixture of tricresyl phosphates containing <0.1% pure TOCP, hypertrophy of the zona fasciculata cells and brown degeneration of cells in the juxtamedullary zone were observed in the adrenal gland. Tricresyl phosphate, a widely used fire-retardant additive for hydraulic fluids, produced minimal to moderate cytoplasmic vacuolization of the adrenal cortex of rats and mice exposed orally for subchronic and chronic durations (NTP 1994). Both tricresyl phosphate and butyl triphenyl phosphate treatment resulted in bilaterally enlarged adrenal glands and lipidosis and vacuolization of the adrenal cortex in rats orally exposed to 400 mg/kg/day for 20-60 days (Latendresse et al. 1994a).

Polyalphaolefin Hydraulic Fluids. No information on endocrine effects in humans or animals following inhalation, oral, or dermal exposure to polyalphaolefin hydraulic fluids was located.

Dermal Effects.

Mineral Oil Hydraulic Fluids. No human studies examining dermal end points were located. In animals, no information on dermal effects following inhalation or oral exposure were located. A number of mineral oil hydraulic fluids have been tested for acute dermal toxicity in rabbits. Signs of skin irritation have been observed following application of a naphthenic petroleum-based hydraulic fluid designated as MIL-H-5606 (Kinkead et al. 1985). No signs of skin irritation were observed following exposure to Sunsafe‘F, Houghto- Safe 5047F, Quintolubric 9583OW, or Pyroguard A-443 (Kinkead et al. 1987a, 1988).

Organophosphate Ester Hydraulic Fluids. No studies regarding dermal effects in humans after inhalation or oral exposure were located. Erythema was observed in humans repeatedly exposed to dermal patches of

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Skydrol 500B-4 for an intermediate duration (Monsanto 1980). Skin scabbing was seen after oral exposure to Sanitizer 154 at 300 mg/kg (IRDC 1981).

Signs of skin irritation were observed in one acute dermal exposure study. A single application of 0.5 mL of Durad 550B resulted in mild erythema and skin thickening in rabbits (FMC 1992a). No signs of skin irritation or evidence of histological damage were observed in rabbits exposed once to Durad 220B, Durad 110, Durad 300, Durad MP280, Durad 125, Fyrquel 220, or cyclotriphosphazene (FMC 1990a, 1991 b; Gaworski et al. 1986; Kinkead et al. 1992a, 1992c, 1992d, 1992e; MacEwen and Vet-not 1985) or after intermediate-duration dermal exposure of rabbits to Fyrquel 220, cyclotriphosphazene, or Cellulube 220 (Carpenter et al. 1959; Kinkead et al. 1989c, 1990; MacEwen and Vet-not 1983). No evidence of skin damage was located in hens ingesting Cellulube 220 for 5 days (Carpenter et al. 1959), or following intermediate-duration inhalation exposure of rats, rabbits, or hamsters to Fyrquel 220 or Durad MP280 (MacEwen and Vemot 1983), rabbits to Cellulube 220 (Carpenter et al. 1959), or rats to cyclotriphosphazene (Kinkead et al. 1989a, 1990).

Polyalphaolejin Hydraulic Fluids. No studies regarding dermal effects in humans following inhalation, oral, or dermal exposure to polyalphaolefin hydraulic fluids were located. Mild skin irritation was observed following a single application of a polyalphaolefin hydraulic fluids designated as DTNSRDC N501 and N5 17. No signs of skin irritation were observed following single applications of polyalphaolefin hydraulic fluids designated as DTNSRDC N448, N518, N525, N527 (MacEwen and Vemot 1983), B85-174 (Kinkead et al. 1987b), or meeting military specifications of MIL-H-83282 (Kinkead et al. 1985) or MIL-H-83282LT (Kinkead et al. 1992b).

Based on these data, it is not likely that acute exposure of humans to environmental levels of polyalphaolefin hydraulic fluids will result in dermal irritation. There is insufficient information to determine if long-term exposure to polyalphaolefin hydraulic fluids will result in dermal irritation in humans.

Ocular Effects.

Mineral Oil Hydraulic Fluids. No human studies examining ocular end points were located. In animals, no information on ocular effects following inhalation or dermal exposure were located. Mild eye irritation was observed in rabbits following a single application of 0.1 mL of Sunsafe F, Houghto-Safe 5047F, Quintolubric

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9583OW, or Pyroguard A-443 (Kinkead et al. 1987a, 1988). No signs of irritation were observed following application of MIL-H-5606 (Kinkead et al. 1985).

Organophosphate Ester Hydraulic Fluids. No studies regarding ocular effects in humans after inhalation or oral exposure were located.

Eye irritation was not observed in animal studies following a single application of 0.1 mL of Fyrquel 220 (Gaworski et al. 1986; Kinkead et al. 1992e), Durad MP280 (Gaworski et al. 1986; Kinkead et al. 1992d), or cyclotriphosphazene (Kinkead et al. 1992c; MacEwen and Vernot 1985). No evidence of eye damage was observed in hens ingesting Cellulube 220 for 5 days (Carpenter et al. 1959), or following intermediateduration exposure of rats, rabbits, or hamsters to aerosols of Fyrquel220 or Durad MP280 (MacEwen and Vet-not 1983), rabbits to Cellulube 220 (Carpenter et al. 1959), or rats to cyclotriphosphazene (Kinkead et al. 1989a, 1990).

Polyalphaolefin Hydraulic Fluids. No studies regarding ocular effects in humans following inhalation, oral, or dermal exposure to polyalphaolefin hydraulic fluids were located. Evidence of eye irritation was observed in rats following a single ocular application or acute exposure to airborne polyalphaolefin hydraulic fluids with a designation of MIL-H-83282LT (Kinkead et al. 1992b). No signs of eye irritation were observed following single ocular applications of polyalphaolefin hydraulic fluids designated as DTNSRDC N448, N501, N517, N518, N525, N528 (MacEwen and Vemot 1983), B85-174 (Kinkead et al. 1987b), or meeting military specifications of MIL-H-83282 (Kinkead et al. 1985) or MIL-H-83282LT (Kinkead et al. 1992b).

Based on these data, it is not likely that acute exposure of humans to environmental levels of polyalphaolefin hydraulic fluids will result in ocular irritation. There is insufficient information to determine if long-term exposure to polyalphaolefin hydraulic fluids will result in ocular irritation in humans.

Body Weight Effects.

Mineral Oil Hydraulic Fluids. There is limited information on body weight effects following exposure to mineral oil hydraulic fluids. No studies were located regarding body weight effects in humans following inhalation, oral, or dermal exposure to mineral oil hydraulic fluids. In rats, no changes in body weight gain were observed following acute inhalation, oral, or dermal exposure to Sunsafe F, Quintolubric 9583OW, Houghto-Safe 5047F, or Pyroguard A-443 (Kinkead et al. 1989b, 1988) and a mineral oil hydraulic fluid

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meeting military specifications of MIL-H-5606 (Kinkead et al. 1985). Body weights of rats exposed to ≤1.0 mg/m^3 of the water-in-oil emulsion hydraulic fluid Houghto-Safe 5047F for 90 days, 23 hours/day, were similar to those of controls (Kinkead et al. 1991). No longer-term studies were located. Based on this limited information, it is not likely that effects on body weight will be observed in humans acutely exposed to environmental levels of mineral oil hydraulic fluids. The likelihood of changes in body weight occurring following longer-term exposure to mineral oil hydraulic fluids is not known.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding body weight effects in humans following inhalation, oral, or dermal exposure to organophosphate ester hydraulic fluids.

Most animal studies found no significant alterations in body weight gain following inhalation, oral, or dermal exposure to a number of organophosphate ester hydraulic fluids. Several studies demonstrated weight loss following acute or intermediate oral exposure to high doses. The identified LOAEL values were 250 mg/kg/day in rats exposed to dibutyl phenyl phosphate for an intermediate duration (Healy et al. 1991), 5,775 mg/kg/day in rats acutely exposed to Durad MP280 (Gaworski et al. 1986) or 10,000 mg/kg and 15,000 mg/kg/day in hens acutely exposed to Reofos 65 or Fyrquel EHC for acute exposures, respectively, (Mortensen and Ladefoged 1992), and 1,333 mg/kg/day in hens exposed to Durad 110 for an intermediate duration (FMC 1986). No changes in body weight gain were observed in rats, rabbits, hamsters, hens, monkeys, or dogs exposed to Fyrquel 220, Skydrol 500B-4, cyclotriphosphazene, a triaryl phosphate hydraulic fluid, Durad MP280 (<5,775 mg/kg/day oral), Durad 550B, Durad 100, Durad 300, Durad 110, Durad 220B, Pydraul 50E, or Pydraul 90E (Ciba-Giegy 1973; FMC 1986, 1990a, 1992a; Gaworski et al. 1986; Healy et al. 1992; Kinkead et al. 1989a, 1989c, 1990, 1992a, 1992c; MacEwen and Vernot 1983, 1985; Monsanto 1979, 1987a, 1987b, 1989; Siegel et al. 1965) via inhalation, oral, or dermal exposure. High oral doses of organophosphate esters have caused body weight changes. In a dose-finding study using 5 pregnant rats per group, a 12% decrease in maternal weight gain was noted after 11 days at 200 mg/kg/day tributyl phosphate (Noda et al. 1994) but in a larger study with 20 animals per group, only minor body weight reductions were observed at 500 mg/kg/day. Several intermediate-duration studies showed reduction in body weight gain in rats or mice. Thirteen-week feeding exposures to tricresyl phosphate in rats at 430 mg/kg/daywere associated with an 11% reduction in body weight in both males and females (NTP 1994). Exposure to 750 mg/kg/day caused a 33% decrease in body weight in male rats. Treatment by gavage for 13 weeks, 5 days a week did not affect female body weight at ≤800 mg/kg/day; male body weight was decreased 13% at this dose (NTP 1994). Body weight effects were also reported in mice in this study, decreases greater than 10% were seen in female mice at 530 mg/kg/day and above and in males at 900 mg/kg/day exposed to tricresyl phosphate by feed

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Gavage doses greater than 400 mg/kg/day also caused decreased body weight (NTP 1994). Dibutyl phenyl phosphate exposure for 91 days at 250 mg/kg/day in female rats was observed to cause a 15% body weight reduction (Healy et al. 1991). Butylated triphenyl phosphate exposure at 1,000 mg/kg/day for 106 days caused an 1 l-17% decrease in body weight in Fischer 344 rats (Latendresse et al. 1994b). Similar results have been reported with exposure to tributyl phosphate in rats: a 15% decrease at 300 mg/kg/day for 18 weeks (Laham et al. 1985) and an 11% decrease at 250 mg/kg/day for 9 weeks (Oishi et al. 1982). Based on these animal data, it is not likely that human exposure to organophosphate ester hydraulic fluids at concentrations expected to be found at or near hazardous waste sites will result in changes in body weight.

Polyalphaolefin Hydraulic Fluids. No information on body weight effects in humans after inhalation, oral, or dermal exposure to polyalphaolefin hydraulic fluids was located. In acute rabbit inhalation, oral, or dermal exposure studies, no changes in growth were observed following exposure to polyalphaolefm hydraulic fluids designated as DTNSRDC N448, N501, N5 17, N518, N525, or N528 (MacEwen and Vemot 1983) B85-174 (Kinkead et al. 1987b), or polyalphaolefin hydraulic fluids meeting military specifications of MIL-H-83282 (Kinkead et al. 1985) or MIL-H-83282LT (Kinkead et al. 1992b). These acute exposure animal studies suggest that short term human exposure to polyalphaolefin hydraulic fluids will not result in alterations of body weight gain. There is insufficient information to determine longer-term human risks.

Immunological and Lymphoreticular Effects.

Mineral Oil Hydraulic Fluids. No information was located regarding immunological effects in humans after inhalation, oral, or dermal exposure to mineral oil hydraulic fluids. Limited animal testing provided no clear evidence that the immune system is a target for mineral oil hydraulic fluids. In guinea pig skin sensitization assays, four of five tested mineral oil hydraulic fluids were inactive as skin sensitization agents, and the remaining fluid only showed weak activity (Kinkead et al. 1985, 1987a, 1988). This information is inadequate to determine the likelihood of immunological effects occurring in humans exposed to environmental media contaminated with mineral oil hydraulic fluids, due to the limited number of immunological end points examined. The data suggest, however, that skin sensitization may not be a major concern with dermal exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding immunological effects in humans or animals after inhalation or oral exposure to organophosphate ester hydraulic fluids. No dermal sensitization reactions were observed in humans exposed to Skydrol 500B-4 for three 24-hour periods per

week for 5 weeks (Monsanto 1980) or in guinea pigs exposed for 10 days to a cyclotriphosphazene-based hydraulic fluid (Kinkead et al. 1992c; MacEwen and Vernot 1985). Thymus weight decreases (both absolute and relative to body weight) were observed, without histological alterations, in rabbits exposed dermally to cyclotriphosphazene for 21 days (Kinkead et al. 1989c, 1990). No histological alterations were observed in the tbymus of rats exposed to aerosols of cyclotriphosphazene for 2 1 days (Kinkead et al. 1989a, 1990). Although there are no data for many organophosphate ester hydraulic fluids, the limited data suggest that skin sensitization may not be a concern with dermal exposure to organophosphate ester hydraulic fluids. High doses (2,905 mg/kg/day) of tricresyl phosphate, a widely used fire-retardant hydraulic fluid additive, produced necrosis of the mandibular lymph node, the spleen, and the thymus in mice exposed by gavage for 16 days (NTP 1994). No such lesions, however, were noted in mice treated with 1,452 mg/kg/day for 16 days or in mice treated with doses $\leq$800 mg/kg/day for 90 days (NTP 1994). A moderate level of tricresyl phosphate, 5 mg/kg/day, in an oral exposure study caused a reduction in serum tetanus antibodies (Banerjee et al. 1992).

Polyalphaolefin Hydraulic Fluids. Two U.S. military polyalphaolefm hydraulic fluids, MIL-H-83232LT and B85-174, produced skin sensitization in guinea pigs (Kinkead et al. 1987b, 1992b), but seven other polyalphaolefin hydraulic fluids did not produce sensitization (Kinkead et al. 1985; MacEwen and Vemot 1983). No other studies were located regarding immunological effects in animals or humans exposed to polyalphaolefm hydraulic fluids. This information suggests that skin sensitization may occur in humans after dermal exposure to MIL-H-83282LT or B85-174, but not after dermal exposure to the other polyalphaolefin hydraulic fluids. The lack of data for other immunological end points precludes determination of the immunotoxicity of polyalphaolef hydraulic fluids.

Neurological Effects.

Mineral Oil Hydraulic Fluids. Peripheral neuropathy developed in a man after about 2 years of heavy occupational exposure by dermal contact to mineral oil hydraulic fluids, at least one of which was known to contain organophosphate esters (0.5% isopropylated triphenyl phosphate and <50 ppm TOCP) (Jarvholm et al. 1986). Subtle electromyographical effects were measured in four of eight men exposed to lower levels of mineral oil hydraulic fluids for 3 months to 13 years (Jarvholm et al. 1986). Other studies regarding neurological effects in humans after exposure to mineral oil hydraulic fluids were not located.

The lack of corroborative case reports, epidemiological data, or animal data (see next paragraph) makes the association between dermal exposure to mineral oil hydraulic fluids and peripheral neuropathy uncertain.

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Nonetheless, the presence of organophosphate esters, some of which are demonstrated neurotoxic agents, in most mineral oil hydraulic fluids (they often are added as anti-wear agents) suggests that they may play a causative role if such an association exists.

Several mineral oil hydraulic fluids (Sunsafe F, Houghto-Safe 5047F, Quintolubric 9583OW, Pyroguard A-443, and MIL-H-5606) produced no clinical signs of neurotoxicity in rabbits after acute occluded dermal exposure (2,000 mg/kg doses), in rats after acute inhalation exposure (110 -210 mg/m^3 for 4 hours or 1,148 mg/m^3 for 6 hours), or in chickens or rats after single gavage dose administration (5,000 mg/kg) (Kinkead et al. 1985,1987a, 1988).

In conclusion, the limited animal and human data suggest that acute to intermediate exposures to mineral oil hydraulic fluids do not represent a major hazard to the neurological health of workers or the general public. The possible presence of low levels of neurotoxic organophosphate esters in these fluids, however, may lead to some concern to limit exposure.

Organophosphate Ester Hydraulic Fluids. Certain organophosphorus compounds produce at least one of two types of acute neurological effects in humans and certain animal species - cholinesterase inhibition associated with acute symptoms including diarrhea, sweating, salivation, respiratory depression and generalized weakness (see Section 2.2.1.4 and Table 2-l 0), and acute organophosphorus-induced delayed neuropathy (OPIDN) associated with the delayed development of incoordination, limb weakness, ataxia and axonal degeneration, and demyelination in spinal cord and peripheral nerve tissues (Abou-Donia and Lapadula 1990; Minton and Murray 1988). Only one study was located examining humans for neurological effects following acute or intermediate exposure to an organophosphate ester hydraulic fluid, and no evidence for the occurrence of neurological effects was found (Baldridge et al. 1959). However, several organophosphate ester hydraulic fluids have produced one or both of these types of neurological effects in animals after acute or intermediate oral, inhalation, or dermal exposures. Other organophosphate ester hydraulic fluids have not produced neurological effects in animal species.

The variability in apparent neurotoxicity among organophosphate ester hydraulic fluids may be influenced by several factors, including differences in phosphate ester composition (including isomeric composition), differences in species' sensitivity to OPIDN, and the fact that the delayed neurotoxicity of certain fluids has only been examined in relatively insensitive species. Several Durad hydraulic fluids (Durads 300,220B, and 550B [FMC 1990a, 1992a]) produced no signs of neurotoxicity in Sprague-Dawley rats after single gavage

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doses of 5,000 mg/kg, but have not been tested in other species. Rats, mice, and rabbits do not display the dysfunctions of OPIDN as seen in humans, cats, dogs, and chickens (Abou-Donia and Lapadula 1990; Baron 1981), and therefore, these fluids have not been adequately tested for their ability to produce OPIDN. It should be noted, however, that a consistent difference in species sensitivity to organophosphate induced cholinesterase inhibition and cholinergic toxicity has not been generally recognized, and rats often have been used to examine the ability of organophosphate esters to inhibit cholinesterases (Wills 1972). In contrast to the previously mentioned Durads, Durad 110 produced no signs of neurotoxicity in rats after single gavage doses of 5,000 mg/kg (FMC 1990a), but produced increased incidences of ataxia in chickens treated with 1,333 mg/kg/day for 28 days or with 90 mg/kg/day for 90 days (FMC 1986). Cellulube 220 is another organophosphate ester hydraulic fluid that demonstrates that species differ in their susceptibility to OPIDN. Signs of delayed neuropathy were observed in goats and cows treated with 5,000 and 7,700 mg/kg doses, respectively, but were not observed in rats given 20,000 mg/kg (Dollahite and Pierce 1969). Rats in this study did not show signs of acetylcholinesterase inhibition, but rabbits given doses of $\geq$ 5,000 mg/kg showed signs of acetylcholinesterase inhibition. Paralysis occurred in rabbits at doses; $\geq$7,500 mg/kg, but the available report did not clearly specify if the observed paralysis was slow in developing or developed quickly (and thus was more closely associated with acetylcholinesterase inhibition).

Humans have been recognized as susceptible to the delayed neuropathy of ingested organophosphorus compounds since the 1930s when it was determined that an epidemic of neuropathies in the southern United States (“ginger jake paralysis”) was caused by the contamination of an alcoholic beverage containing an extract of Jamaican ginger (“ginger jake”) with tri-*ortho* -cresyl phosphate (TOCP) (Smith et al. 1930). This is an isomer of the hydraulic fluid component tricresyl phosphate. While current manufacturing processes minimize production of this isomer, it is possible that older organophosphate ester hydraulic fluids disposed of at waste sites may be contaminated with TOCP. The chicken generally is considered one of the most sensitive animal species to OPIDN, and neurotoxicity testing in hens is a normal practice in the safety evaluation of organophosphate esters used in plasticizers, hydraulic fluids, and insecticides (Johnson 1982).
The diversity in the ability of organophosphate ester hydraulic fluids to produce OPIDN is best illustrated by the database for acute delayed neuropathy in chickens after oral exposure. Several organophosphate hydraulic fluids produced definitive OPIDN in chickens after acute gavage exposure (Cellulube 220, Durad MP280, and Fyrquels EHC, 150, and 220), while other fluids produced other neurological effects (Skydrol LD-4 and 500B-4, Reofos 65: cholinergic toxicity and spinal cord lesions without signs of delayed neuropathy). Another group produced no neurological effects in chickens (several U.S. military fluids designated as MIL-H-19457C and Pydrauls 29ELT, 50E, and 90E). Thus, a definitive conclusion that acute,

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intermediate, or chronic oral exposure to organophosphate ester hydraulic fluids, as a class, can produce neurotoxic effects cannot be drawn. There should be a concern, however, that acute, intermediate, or chronic oral exposure to any particular fluid demonstrated to be neurotoxic in chickens (or other animal species) also may produce neurological effects in humans at appropriate dosage levels.

Diverse neurological effects have been observed in animals after acute to intermediate inhalation or dermal exposure to organophosphate hydraulic fluids. Observed effects from inhalation include mild transient lethargy in rabbits after 4-hour exposures to U.S. military fluids designated as Durad MP280 (6,190 mg/m^3) and Fyrquel 220 (5,750 mg/m^3) (Gaworski et al. 1986; Kinkead et al. 1992a); salivation (possibly of neurological origin) in rats exposed to 300 mg/m^3 Skydrol 500B-4,6 hours/day for 6 or 13 weeks (Healy et al. 1992; Monsanto 1987a, 1987b, 1989); head droop, generalized weakness, and decreased blood cholinesterase in rabbits exposed to Cellulube 220 at 2,000 mg/m^3, 4 hours/day for $\leq$22 days (Carpenter et al. 1959), delayed neuropathy in rabbits and chickens continuously exposed for 30-l 60 days to another U.S. military hydraulic fluid (triaryl phosphate) at 102 mg/m^3 and 23 mg/m^3, respectively (Siegel et al. 1965); and kyphosis in rats continuously exposed to 100 mg/m^3 concentrations of Durad MP280 or Fyrquel 220 for 90 days (McEwen and Vemot 1983). Observed effects from dermal exposure include delayed neuropathy in cattle after dermal treatment with the waste from reclamation of a Fyrquel hydraulic fluid (Julian et al. 1976) and cholinergic toxicity in rabbits following occluded dermal exposure to Cellulube 220 (Carpenter et al. 1959).

The range of responses noted for the different fluids, as well as the absence of inhalation or dermal data for many organophosphate hydraulic fluids known to be manufactured, makes it difficult to conclude whether inhalation or dermal exposure to organophosphate fluids, as a class, will produce neurological effects in humans. As with oral exposure, however, there should be a concern that dermal or inhalation exposure to any particular organophosphate fluid demonstrated to produce neurological effects (either cholinesteraseinhibition-associated effects or delayed neuropathic effects) in animals may also produce neurological effects in humans at an appropriate dosage level.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding neurological effects in humans after inhalation, oral, or dermal exposure to polyalphaolefin hydraulic fluids.

Single gavage doses (4,250-5,000 mg/kg) of several polyalphaolefin hydraulic fluids produced no signs of neurotoxicity in rats within 14 days of dosing (Kinkead et al. 1987b, 1985, 1992b; MacEwen and Vemot

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1983) or chickens within 21 days of dosing (Kinkead et al. 1985, 1992b). Several polyalphaolefin hydraulic fluids produced lethargy in some rabbits during 24-hour periods of exposure to occluded dermal doses of ≈1,700 mg/kg (MacEwen and Vemot 1983). Lethargy was also observed in rats during and after 4-hour inhalation exposures to lethal concentrations of several polyalphaolefin hydraulic fluids ranging from 700 to 6,430 mg/m^3 (Kinkead et al. 1987b; MacEwen and Vemot 1983).

In general, the animal data do not provide strong evidence that acute exposures to polyalphaolefin hydraulic fluids produce neurological effects. No information is available regarding neurological effects after intermediate or chronic exposure to polyalphaolefin hydraulic fluids.

Reproductive Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding reproductive effects in humans or animals after inhalation, oral, or dermal exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal exposure to organophosphate ester hydraulic fluids.

Organophosphate ester hydraulic fluids may cause adverse reproductive effects based on observations of testicular atrophy in rats after continuous inhalation exposure to 101 mg/m^3 Durad MP280 for 90 days (MacEwen and Vemot 1983), loss of spermatic elements and degeneration in the seminiferous tubules in dogs given 20 subcutaneous injections of Cellulube 220 at doses ranging from 100 to 500 mg/kg/day (Carpenter et al. 1959), and decreased lactation and delayed estrus in cows after oral ingestion of Fyrquel-150-contaminated plant tissue at unspecified dose levels (Beck et al. 1977).

Examination of reproductive organs found no histological alterations in male or female rats exposed to aerosol concentrations of cyclotriphosphazene ≤990 mg/m^3, 6 hours/day, 5 days/week for 21 days (Kinkead et al. 1989a, 1990); in male or female rats exposed to Skydrol500B-4 concentrations ≤300 mg/m^3, 6 hours/day, 5 days/week for 13 weeks (Healy et al. 1992; Monsanto 1987a, 1987b, 1989). No gross alterations were observed in male or female rats continuously exposed to 100 mg/m^3 Fyrquel 220 for 90 days (MacEwen and Vemot 1983); in male or female rabbits and male hamsters continuously exposed to 101 mg/m^3 Durad MP280 or 100 mg/m^3 Fyrquel 220 for 90 days (MacEwen and Vemot 1983); and in male rabbits exposed to Cellulube 220 aerosol concentrations of 2,000 mg/m^3, l-4 hours/day, 4-5 days/week for

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≤26 days (Carpenter et al. 1959). There were also no gross alterations found following acute oral exposure of rabbits to Cellulube 220 at doses 5480 mg/kg/day (Carpenter et al. 1959) or in leghorn hens exposed to MLH-19457C or MLH-19457B fluids at doses ≤420 mg/kg/day for 5 days (Kinkead et al. 1989b); or dermal exposure of male rabbits to unspecified doses of Cellulube 220 for l-4 hours/day, 4-5 days/week for ≤43 days (Carpenter et al. 1959); or in male or female rabbits exposed to 1,000 mg/kg dermal doses of cyclotriphosphazene 6 hours/day, 5 days/week for 2 1 days (Kinkead et al. 1989c, 1990). No exposurerelated changes in gonad weights were observed in male rats following dietary exposure to 50 mg/kg/day Pydraul 90E doses for 90 days (Monsanto 1979). Studies designed to assess reproductive performance in animals after exposure to organophosphate ester hydraulic fluids were not located.

An organophosphate ester commonly used in hydraulic fluids, tricresyl phosphate (TCP), and tri-*ortho*-cresyl phosphate (TOCP), a possible contaminant of older formulations of TCP, have been shown to alter testicular morphology, testicular function, and reproductive function in rodents after oral exposure (Carlton et al. 1987; Chapin et al. 1988; NTP 1994; Somkuti et al. 1987a, 1987b).

In studies conducted by Somkuti et al. (1987a, 1987b), significant reductions in sperm density and motility, altered morphology (e.g., headless sperm, spermatozoa with no head hook or excessive hooks, and amorphous heads), and decreased relative testicular weight were observed in rats given oral doses of TOCP. The effects were dose- and duration-related. No sperm effects were observed in rats exposed to 150 mg/kg/day for 3 or 7 days, but longer exposure resulted in decreased sperm count (≥10 days) and motility (≥14 days) (Somkuti et al. 1987b). In rats exposed to doses ≥50 mg/kg/day TOCP for 63 days, sperm had altered morphology and no motility, and relative testicular weight was decreased, compared with controls (Somkuti et al. 1987a). In addition to these effects, degeneration and necrosis of the seminiferous epithelium were observed in rats exposed to ≥100 mg/kg/day TOCP for 14 days (Somkuti et al. 1987a) and disorganization of testicular germ cells and the presence of hematoxylin-positive “droplets” in the tubule lumena were observed in rats exposed for 63 days to ≥25 mg/kg/day TOCP (Somkuti et al. 1987a). No evidence of seminiferous tubule regeneration or re-initiation of spermatogenesis was observed 98 days after termination of the 21 -day exposure period (Somkuti et al. 1987b).

No changes in testicular testosterone concentrations were observed in rats exposed to 150 mg/kg/day TOCP for 3-21 days or 100 mg/kg/day for 63 days. Significant decreases in testicular nonspecific esterase (NSE) activity and neurotoxic esterase (NTE) activity were observed in rats exposed to ≥10 and ≥50 mg/kg/day, respectively, for 63 days (Somkuti et al. 1987a). Testicular activities of nonspecific esterase and neurotoxic

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esterase were also inhibited in rats exposed to 150 mg/kg for ≥3 days. No changes in testicular ß-glucuronidase (Serotoli cell-specific enzyme) or serum luteinizing hormone, follicle stimulating hormone, or testosterone levels were observed (Somkuti et al. 1987b).

In contrast to TOCP, exposure of rats to tri-para-cresyl phosphate (TPCP) for 63 days, at oral doses of 100 mg/kg/day, did not significantly alter (compared with controls) the frequency of sperm with abnormal morphology, relative testis weight, sperm motility, sperm density, or testicular activities of NSE (also known as butyrylcholinesterase) and NTE (Somkuti et al. 1987a). Acetylcholinesterase activity was not detected in testicular homogenates (either controls or treated) in these studies (Somkuti et al. 1987a). The negative data for TPCP, coupled with the positive data for TOCP, suggest that the testicular toxicity of TOCP may involve inhibition of esterases in the testis. Molecular details of this potential involvement, however, are unknown, as are the physiological functions of NSE and NTE. Light and electron microscopic studies of rats during exposure to TOCP have identified the Sertoli cell as the first cell type that is structurally altered in the testis (Somkuti et al. 1991). Studies with Sertoli cells in culture showed that exposure for 24 hours to saligenin cyclic-*ortho*-tolyl phosphate (the TOCP metabolite thought to be responsible for TOCP delayed neuropathy), but not TOCP, produced a dose-related decrease in NSE activity (NTE activity was not measured in these studies) (Chapin et al. 1991). Several other TOCP metabolites did not decrease NSE activity in cultured Sertoli cells (Chapin et al. 1991). The presence of TOCP in the culture medium of rat Sertoli cells produced diminished NSE activities only when the cells were co-cultured with Leydig cells (Chapin et al. 1990). These results have led to the hypothesis that the in viva metabolic conversion of TOCP to saligenin cyclic-*ortho*tolyl phosphate in the testis may occur in Leydig cells.

Sperm alterations have also been observed in rats receiving repeated gavage doses of a mixture of TCP isomers (containing < 9% TOCP). Decreased sperm motility, concentration, and velocity were observed in rats receiving 200 mg/kg/day TCP in corn oil for 66 days (Carlton et al. 1987). These effects were not observed in the vehicle-control or 100 mg/kg/day groups. A dose-dependent increase in abnormal sperm morphology was observed in the 100 and 200 mg/kg/day groups. In the 200 mg/kg/day group, there was a significant reduction in epididymal weights. Significant increases in minimal-to-mild seminiferous tubule necrosis and degeneration, hypospermia in the epididymides, degenerate and immature spermatids in seminiferous tubules and epididymides, and early sperm granulomas in the seminiferous tubules were observed in the 200 mg/kg/day males. Reproductive effects were also observed in female rats exposed to TCP. A dose-dependent diffuse vacuolar cytoplasmic alteration of ovarian interstitial cells and an impression of increased follicular and luteal activity (as indicated by increased numbers of follicles and corpora lutea)

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were observed in female rats receiving daily gavage doses of 200 or 400 mg/kg/day TCP (Carlton et al. 1987).

A mixed isomer preparation of TCP (containing <0.1% tri-*ortho*-cresyl phosphate) produced histological changes in reproductive organs in both sexes of rats and female mice in 13-week and 2-year bioassays (NTP 1994). Ovarian interstitial cell hypertrophy occurred in female mice and female rats exposed to gavage doses of 50-800 mg/kg/day for 13 weeks, in female rats exposed to dietary doses of 65 and 120 ng/kg/day for 13 weeks, and in female rats exposed to dietary doses of 9 or 18 mg/kg/day for 2 years (NTP 1994). Atrophy of the seminiferous tubules occurred in male rats that received gavage doses of 400 and 800 mg/kg/day for 13 weeks and in male rats exposed to dietary doses of 470 and 940 mg/kg/day for 13 weeks (NTP 1994).

Reproductive performance has also been assessed in animals exposed to mixed isomers of TCP. Male rats were gavaged daily with 100 or 200 mg/kg/day TCP (containing <9% TOCP) during a 56-day premating and 10-day mating period. The males were mated with female rats exposed to TCP 14-days prior to mating, during the 10-day mating, 21 -day gestation, and 21 -day lactation periods. Males exposed to 100 mg/kg/day were mated with females exposed to 200 mg/kg/day, and 200 mg/kg/day males were mated with 400 mg/kg/day females. No difference in numbers of sperm-positive females was observed. However, significant decreases in the number of females delivering live young, litter size, and pup viability were observed in the high-dose group (Carlton et al. 1987).

No changes in the fertility index (number of dams producing a litter per number of breeding pairs) were observed in mice exposed to 0, 62.5, 124, or 250 mg/kg/day TCP (containing <0.1% TOCP) in the diet for 98 days in a continuing breeding experiment (Chapin et al. 1988). However, a significant increase in the number of dead pups and decrease in the number of live pups were observed in the 250 mg/kg/day group. A significant increase in the number of dead pups was also observed in the last two litters of mice exposed to 124 mg/kg/day. The last litters from the 0, 62.5, and 124 mg/kg/day groups were fed TCP from weaning to day 74 of age. At this point, they were mated. Significant trends toward decreased mating and fertility indices and number of live pups per litter were observed. In the 124 mg/kg/day group, the fertility index and proportion of live pups per litter were significantly lower than in the control group. Sperm-motility was significantly decreased in both TCP-exposed groups, and no change in epididymal sperm concentration or histological alterations in reproductive organs were observed.

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To further assess the reproductive toxicity of TCP, a cross-over fertility test was performed (Chapin et al. 1988). Control males were mated to females exposed to 250 mg/kg/day, and males exposed to 250 mg/kg/day were mated with control females. The number of live pups per litter was significantly decreased in both groups of exposed mice. The reproductive performance was more severely affected in the exposed females mated with control males. No treatment related changes were observed in the prostate, seminal vesicles, ovaries, uterus, or vagina. In mice exposed to 250 mg/kg/day, atrophy of the seminiferous tubules was seen in the testes, and significant decreases in testicular and epididymal weights were observed. Significant decreases in the percentage of motile sperm, sperm concentration, and the percentage of abnormal sperm were observed in the 250 mg/kg/day group. Latendresse et al. (1994b) reported decreased numbers of litters in rats exposed by gavage to 600, 1,000, and 1,700 mg/kg/day butylated triphenyl phosphate. In the same study, abnormal estrous cycles and decreased uterine weights were noted in female rats exposed to 1,000 mg/kg/day butylated triphenyl phosphate.

An *in vitro* study demonstrated decreased testosterone output by Leydig cells with addition of TOCP (Chapin et al. 1990), and suggested that the TOCP metabolite, saligenin cyclic-o-tolyl phosphate, may be the responsible agent for eliciting this effect.

Only three (Durad MP280, Cellulube 220, and Fyrquel 150) of nine hydraulic fluids that have been studied in animals produced reproductive effects. It is difficult to generalize about the ability of organophosphate ester hydraulic fluids, as a class, to cause reproductive effects in humans because of the inadequacies of the database. There are no human data. Examinations of reproductive organs in animals after exposure have been conducted for only nine organophosphate hydraulic fluids. In addition, reproductive performance has not been evaluated following exposure of animals to organophosphate ester hydraulic fluids. Nevertheless, the limited data suggest that some hydraulic fluids in this class may produce reproductive effects, while other may not. For example, Durad MP280 produced testicular atrophy in rats via inhalation exposure, but Fyrquel 220 did not (MacEwen and Vemot 1983). Tri-*ortho*-cresyl phosphate and mixed isomer preparations of TCP can be found in hydraulic fluids and are demonstrated reproductive toxicants in animals. In general, the limited data suggest that exposure to certain organophosphate ester hydraulic fluids, especially those containing TCP isomers, may present a reproductive hazard to public health at some undetermined dosage level.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding reproductive effects in humans or animals after inhalation, oral, or dermal exposure to polyalphaolefin hydraulic fluids.

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Developmental Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding developmental effects in humans or animals after inhalation, oral, or dermal exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding developmental effects in humans after inhalation, oral, or dermal exposure to organophosphate ester hydraulic fluids.

Data concerning developmental toxicity in animals are very limited, and are at best suggestive that elicitation of developmental effects by some organophosphate ester hydraulic fluids may occur in some animals. The developmental toxicity data are too sparse to make any conclusions regarding their relevance to human health.

Data that are suggestive of adverse developmental effects in animals after an assumed acute oral exposure to an organophosphate ester hydraulic fluid are restricted to an observation in cows of retarded growth in calves of cows with reduced lactation, and abnormal growth in one calf of a cow that showed moderate ataxia, after the cows ingested grass probably contaminated with components of Fyrquel 150 (Beck et al. 1977).

None of the calves of 10 cows were adversely affected after the cows were acutely dermally exposed to an unknown quantity of a Fyrquel hydraulic fluid reclamation waste that probably contained TOCP and other hydraulic fluid components and was applied liberally to their backs once (Julian et al. 1976).

Dibutyl phenyl phosphate, a component of some organophosphate ester hydraulic fluids, decreased the postnatal survival of rat pups. Decreased survival to day 4 was observed in the F_{1a} pups (first litter) of rats exposed to 50 or 250 mg/kg/day and F_{1b} pups (second litter) of rats exposed to 5 or 50 mg/kg/day (but not to 250 mg/kg/day). The number of live offspring at weaning was also diminished in the F_{1a} pups in 50 and 250 mg/kg/day groups and F_2 pups of the 250 mg/kg/day group. In an attempt to determine if the reduced survival was due to *in utero* effects, the F_{1b} pups of the 250 mg/kg/day pups were cross-fostered with control pups. Reduced survival at day 4 and weaning was observed in the control pups raised by the high-dose rats. Decreased body weight gains were observed in the F_0 dams (parental) exposed to 250 mg/kg/day and F_1 dams exposed to 50 and 250 mg/kg/day. Effects on control pups, potentially exposed via treated dams are equivocal. Although survival was reduced, the cause is not clear (Healy et al. 1991).

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Additionally, no changes were seen in the type or incidence of developmental anomalies observed in the pups of male and female rats that had been orally exposed to triphenyl phosphate, another component of some organophosphate ester hydraulic fluids at doses ≤690 mg/kg/day for 91 days, including through mating and gestation (Welsh et al. 1987).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding developmental effects in humans or animals after inhalation, oral, or dermal exposure to polyalphaolefin hydraulic fluids.

Genotoxic Effects.

Mineral Oil Hydraulic Fluids. No studies were located regarding genotoxic effects in humans or animals after inhalation, oral, or dermal exposure to mineral oil hydraulic fluids. No information was located regarding the genotoxicity of mineral oil hydraulic fluids in *in vitro* assays.

Organophosphate Ester Hydraulic Fluids. No studies were located regarding genotoxic effects in humans after inhalation, oral, or dermal exposure to organophosphate ester hydraulic fluids.

No studies were located regarding genotoxic effects in animals after inhalation or dermal exposure to organophosphate ester hydraulic fluids. However, the incidence of nuclear anomalies in bone marrow interphase cells was significantly increased in Chinese hamsters gavaged on 2 consecutive days with 2,500 and 5,000 mg/kg/day of Reofos 50 (Ciba-Geigy 1984a), but not in those dosed with 1,250 mg/kg/day.

Oral doses of ≤5,000 mg/kg Reofos 50 or Reolube HYD46 to male and female Chinese hamsters did not induce significant increases in sister chromatid exchanges in bone marrow cells (Ciba-Geigy 1983b, 1984b).

No results indicating genotoxicity were observed in *in vitro* studies that examined six organophosphate ester hydraulic fluids for gene mutation, deoxyribonucleic acid (DNA) damage, or chromosomal aberrations in eukaryotes (see summarized data in Table 2-l 1).

No mutagenic activity was observed in Ames assays of the prokaryote *Salmonella typhimurium* either with or without activation systems when exposed to concentrations of Durad 550B ≤10,000 mg/plate (FMC 1992b), Reofos 95 at concentrations ≤162 µg/plate (Ciba-Geigy 1978a), Reofos 50 at concentrations ≤162 µg/plate (Ciba-Geigy 1978b), or Reolube HYD46 at concentrations ≤5,120 µg/plate (Ciba-Geigy

Table 2-11. Genotoxicity of Organophosphate Ester Hydraulic Fluids *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Prokaryotic organisms:					
Salmonella typhimurium (Ames assay)	Gene mutation	–	–	FMC 1992b	Durad 550B
S. typhimurium (Ames assay)	Gene mutation	–	–	Ciba-Geigy 1978a	Reofos 95
S. typhimurium (Ames assay)	Gene mutation	–	–	Ciba-Geigy 1983a	Reolube HYD 46
S. typhimurium (Ames assay)	Gene mutation	–	–	Ciba-Geigy 1978b	Reofos 50
S. typhimurium (Ames assay)	Gene mutation	–	–	NTP 1994	Tricresyl phosphate
Eukaryotic organisms:					
Mammalian cells:					
Rat hepatocytes (DNA-repair Assay)	DNA damage	No data	–	Ciba-Geigy 1984c	Reolube HYD 46
Rat hepatocytes (DNA-repair Assay)	DNA damage	No data	–	Ciba-Geigy 1984d	Reofos 50
Chinese hamster CHO cells	Chromosomal aberrations	–	–	Monsanto 1988a	Skydrol 500 B-4
Chinese hamster CHO cells	Chromosomal aberrations	–	–	Monsanto 1988b	Skydrol LD-4
Chinese hamster CHO cells	Chromosomal aberrations	–	–	NTP 1994	Tricresyl phosphate

– = negative result; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid

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1983a). Tricresyl phosphate, a component of some hydraulic fluids, was not mutagenic in *S. typhimurium* strains TAlOO, TA1535, TA1537, or TA98 (NTP 1994) (see Table 2-l 1).

DNA-repair assays of rat hepatocytes treated with Reolube HYD46 at concentrations < 150 nL/mL (Ciba-Geigy 1984c) or Reofos 50 at concentrations ≤75 nL/mL (Ciba-Geigy 1984d) were negative. Assays that examined Chinese hamster ovary cells for chromosomal aberrations (with or without activation systems) were negative after *in vitro* exposure to Skydrol 500B-4 or Skydrol LD-4 at concentrations ≤95 µg/mL (Monsanto 1988a, 1988b). Tricresyl phosphate did not induce chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells (NTP 1994).

The studies indicate low genotoxic potential in five of six organophosphate ester hydraulic fluids, and the data that suggest genotoxic potential in Reofos 50 appear to be equivocal. The incidence of nuclear anomalies was reportedly increased in bone marrow interphase cells of Chinese hamsters after acute oral exposure to Reofos 50 (Ciba-Geigy 1984a). However, the incidence of sister chromatid exchanges in bone marrow cells of Chinese hamsters after oral exposure to the same oral dose levels of Reofos 50 (≤5,000 mg/kg by gavage) did not differ from the incidence observed in controls (Ciba-Geigy 1984b). The negative *in vitro* genotoxicity results of an Ames assay with *S. typhimurium* (Ciba-Geigy 1978b) and a DNA-repair assay with rat hepatocytes (Ciba-Geigy 1984d) further suggest that Reofos 50 is a very weak genotoxin if it is genotoxic at all.

Polyalphaolefin Hydraulic Fluids. No studies were located regarding genotoxic effects in humans or animals after inhalation, oral, or dermal exposure to polyalphaolefin hydraulic fluids. No information was located regarding the genotoxicity of polyalphaolefin hydraulic fluids in *in vitro* assays.

Cancer. The Department of Health and Human Services (DHHS), the International Agency for Research on Cancer (IARC), and EPA have not classified mineral oil hydraulic fluids, polyalphaolefin hydraulic fluids, and organophosphate ester hydraulic fluids for carcinogenic effects.

Mineral Oil Hydraulic Fluids. No associations between occupational exposure to mineral oil hydraulic fluids and cancer occurrence in particular organs were found in a case-control study of cancer patients after adjustment for gasoline exposure (Siemiatycki et al. 1987a). No other studies were located regarding cancer in humans or animals after inhalation, oral, or dermal exposure to mineral oil hydraulic fluids. The available animal and human data are inadequate to ascertain the human carcinogenicity of mineral oil hydraulic fluids.

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There is evidence, as reviewed by IARC (1984), that certain types of mineral oils are carcinogenic in animals and other mineral oils are not carcinogenic. The carcinogenic activity of mineral oils is thought to be dependent upon the initial processing of the crude petroleum and the nature and concentration of additives. Thus, highly refined oils like white mineral oil do not appear to be carcinogenic, but carcinogenic responses have been observed in animals exposed to untreated vacuum distillates of petroleum and mildly solventrefined or mildly hydro treated oils (IARC 1984). In addition, carcinogenic responses have been observed in animals exposed to used gasoline engine oils (IARC 1984). The available data for mineral oils as a class are not adequate to predict whether a particular mineral oil hydraulic fluid will be carcinogenic because of the dependence of carcinogenic activity upon quality of the oil, the presence of additives, and potentially, the conditions of use (IARC 1984).

Organophosphate Ester Hydraulic Fluids. No studies were located regarding cancer in humans or animals after inhalation, oral, or dermal exposure to organophosphate ester hydraulic fluids. In 2-year feed studies, carcinogenic responses to tricresyl phosphate, a common fire-retardant, organophosphate ester hydraulic fluid additive, were not found in male or female Fischer 344 rats exposed to daily doses $\leq$20 mg/kg/day or in male or female B6C3F_1, mice at doses $\leq$45 mg/kg/day (NTP 1994). Dietary administration of tributyl phosphate was associated with transitional and squamous cell carcinomas of the bladder in rats after 2 years of exposure at 143.3 mg/kg/day (FMC 1994a). An increased incidence of hepatocellular adenomas in the liver was observed in mice after dietary administration of 455 mg/kg/day tributyl phosphate for 18 months (FMC 1994b).

Polyalphaolefin Hydraulic Fluids. No studies were located regarding cancer in humans or animals after inhalation, oral, or dermal exposure to polyalphaolefin hydraulic fluids.

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NRC 1989). The preferred

biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to hydraulic fluids are discussed in Section 2.6.1. Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by hydraulic fluids are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Hydraulic Fluids

Mineral Oil Hydraulic Fluid. Limited studies were located that suggest biomarkers of exposure to mineral oil hydraulic fluids. No data that indicate quantitative or qualitative biomarkers of exposure to mineral oil hydraulic fluid were located. Mineral oil (hydrocarbons containing ≈15-30 carbon atoms per molecule) is a major component that is common to all mineral oil hydraulic fluids. Following exposure to food-grade mineral oil, most of the administered radioactivity was excreted in the feces as mineral oil (Ebert

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et al. 1966). Although the presence of mineral oil is a biomarker of exposure to mineral oil hydraulic fluids, it is also a biomarker of exposure to other readily available products that contain mineral oils.

Organophosphate Ester Hydraulic Fluid. Analyses of blood or urine for the presence of organophosphates or their metabolites can be valuable in confirming exposure to organophosphate ester hydraulic fluids; however, sample collections must be completed during or shortly after exposure unless exposure levels are very high. Urinary excretion of metabolites can be completed within a few days of exposure, depending on the level of exposure.

The inhibition of two cholinesterase activities in blood can also be used to confirm exposure to certain organophosphate ester compounds. Red blood cell acetylcholinesterase is the same cholinesterase found in the gray matter of the central nervous system and motor endplates of sympathetic ganglia. Synonyms for this enzyme include specific cholinesterase, true cholinesterase, and E-type cholinesterase. Plasma cholinesterase is a distinct enzyme found in intestinal mucosa, liver, plasma, and white matter of the central nervous system. Synonyms for this enzyme include nonspecific cholinesterase, pseudocholinesterase, butyrylcholinesterase, and S-type cholinesterase (Evans 1986). Nonspecific cholinesterase is thought to be a very poor indicator of neurotoxic effects.

A third enzyme may have limited potential as a measure of exposure. Neurotoxic esterase, also known as neuropathy target esterase (NTE), is inhibited by certain organophosphate esters. When brain NTE is inhibited above 70% for acute or possibly as low as 50% for repeated exposures, there is a consensus that delayed neuropathy is likely. NTE also is found in lymphocytes and platelets (Lotti et al. 1984). The measurement of lymphocytic NTE or platelet NTE has been proposed as a surrogate for brain NTE (Lotti et al. 1984; Maroni and Bleeker 1986). Monitoring lymphocyte NTE in agricultural workers exposed to organophosphate insecticides for inhibition of lymphocyte NTE, however, has not been widely employed because of a number of practical limitations, including the instability of the enzyme in blood and the possibility that lymphocyte proliferation, in response to infection, may influence activity measurements (Mutch et al. 1992).

Measurement of inhibition of blood cholinesterases requires estimation of baseline values because “normal” values vary widely among individuals due to genetic, age, sex, and disease-related variance (Coye et al. 1986; Shanor et al. 1961). In the absence of baseline values for an individual, a consistent increase in activity with time after cessation of exposure can be used to confirm exposure (Evans et al. 1986). Plasma cholinesterase

activity is more labile than red blood cell acetylcholinesterase, can be depressed by hepatic disease, infection, alcohol consumption, and pregnancy, and is often more sensitive to inhibition by organophosphates than is acetylcholinesterase (Trundle and Morcial 1988). Plasma cholinesterase is produced in the liver and can be rapidly regenerated. Red blood cell acetylcholinesterase activity can be depressed by hemolytic anemia. It should be noted that organophosphate insecticides and carbamate insecticides inhibit both types of blood cholinesterase. Thus, inhibition of red cell cholinesterase alone is not sufficiently diagnostic to ascertain exposure to organophosphate ester hydraulic fluids, per se.

Decreased levels of erythrocyte acetylcholinesterase and/or plasma butyrylcholinesterase, brain neurotoxic esterase, or clinical signs of cholinesterase inhibition have been observed in animals exposed to Cellulube 220 (Carpenter et al. 1956; Dollahite and Pierce 1969), Skydrol500B-4 (Healy et al. 1992; Monsanto 1987d), Skydrol LD-4 (Monsanto 1987c), Fyrquel EHC (Stauffer Chemical Co. 198 l), Fyrquel220 (Gaworski et al. 1986; Kinkead et al. 1992a), Fyrquel 150 (Beck et al. 1977), Durad MP280 (Gaworski et al. 1986; Kinkead et al. 1992d), and Durad 125 (FMC 1991). There are insufficient data to establish an exposure-response relationship for cholinesterase inhibition for the individual hydraulic fluids in this class.

Polyalphaolefin Hydraulic Fluid. Data were insufficient to indicate biomarkers of exposure to polyalphaolefin hydraulic fluids.

2.6.2 Biomarkers Used to Characterize Effects Caused by Hydraulic Fluids

Mineral Oil Hydraulic Fluid. Data were insufficient to indicate biomarkers of effects caused by mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluid. The most widely examined target of organophosphate ester hydraulic fluids is the nervous system. Two types of neurological effects have been observed following exposure to certain organophosphate ester hydraulic fluids: cholinergic symptoms associated with acetylcholinesterase inhibition and delayed neuropathy (OPIDN).

Inhibition of cholinesterase activity in red blood cells (erythrocyte acetylcholinesterase) provides a biomarker for cholinergic toxic effects caused by organophosphate esters in hydraulic fluids. As stated previously, baseline levels of this enzyme for an individual must be known in order to use inhibition as a biomarker of effect because “normal” values vary widely among humans (Coye et al. 1986; Evans 1986). Cholinesterase

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activities in agricultural workers chronically exposed to organophosphate and carbamate insecticides are routinely monitored in the United States to prevent development of cholinergic toxic effects. In general, the inhibition of erythrocyte acetylcholinesterase has been shown to correlate with the appearance of cholinergic symptoms such as salivation, diarrhea, altered heart rate and rhythm, respiratory depression, dizziness, and confusion (Coye et al. 1986). However, the rate of decline in enzyme activity is taken as a better indicator of the development of overt effects than is the absolute level of inhibition. Cholinergic symptoms may not develop in chronically exposed workers with 70-80% inhibition, but may develop in individuals without prior exposure after sudden exposure and a rapid decrease in cholinesterase activities of <30% (Coye et al. 1986). Inhibition of red blood cell acetylcholinesterase is generally taken to be a better indicator of effect than plasma cholinesterase, because acetylcholinesterase is the same enzyme as that found in nervous tissue, and inhibition of plasma cholinesterase sometimes has not correlated with the appearance of cholinergic symptoms (Coye et al. 1986; Peedicayil et al. 1991).

Cholinergic effects have been observed in animals exposed to Cellulube 220 (Carpenter et al. 1956; Dollahite and Pierce 1969), Skydrol 500B-4 (Healy et al. 1992; Monsanto 1987d), Skydrol LD-4 (Monsanto 1987c), Fyrquel EHC (Stauffer Chemical Co. 1981), Fyrquel220 (Gaworski et al. 1986; Kinkead et al. 1992a), Fyrquel 150 (Beck et al. 1977), Durad MP280 (Gaworski et al. 1986; Kinkead et al. 1992d), and Durad 125 (FMC 1991). In many cases, whole blood cholinesterase activity was measured instead of erythrocyte acetylcholinesterase in these studies. Thus, there are insufficient data to establish a relationship between severity of effects and percent inhibition of blood cholinesterase activity for the organophosphate ester hydraulic fluids. In other words, plasma cholinesterase inhibition is a biomarker of exposure, but not of effect.

Organophosphate-induced delayed neurotoxicity (OPIDN) is a slowly developing axonal degeneration and demyelination in central and peripheral nerve tissues. The initial symptoms occur 8-14 days or longer after exposure to organophosphate (Ecobichon 1991; Johnson 1975; Murphy 1986) and can occur after a single exposure. Inhibition of brain neurotoxic esterase (NTE) has been proposed as a biomarker for OPIDN (Ecobichon 1991). The measurement of lymphocytic NTE or platelet NTE has been proposed as a surrogate for brain NTE (Lotti et al. 1984; Maroni and Bleeker 1986). Monitoring lymphocyte NTE in-agricultural workers exposed to organophosphate insecticides for inhibition of lymphocyte NTE, however, has not been widely employed because of a number of practical limitations, including the instability of the enzyme in blood and the possibility that lymphocyte proliferation, in response to infection, may influence activity measurements (Mutch et al. 1992). Acetylcholinesterase in nerve tissue is not thought to be directly involved in OPIDN because of a lack of correlation between acetylcholinesterase inhibition and potency as a OPIDN

agent (Johnson 1975, 1990; Murphy 1986). OPIDN has been observed in animals exposed to unspecified triaryl phosphate hydraulic fluid (Siegel et al. 1965), Cellulube 220 (Carpenter et al. 1959; Dollahite and Pierce 1969), Fyrquel EHC (Mortensen and Ladefoged 1992; Stauffer 1980), Durad MP280 (Gaworski et al. 1986), and Reofos 65 (Mortensen and Ladefoged 1992).

Polyalphaolefin Hydraulic Fluid. Data were insufficient to indicate biomarkers of exposure to polyalphaolefin hydraulic fluids.

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

2.7 INTERACTIONS WITH OTHER CHEMICALS

No studies were located regarding interactions of mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, or polyalphaolefin hydraulic fluids with other substances.

However, there are some data on interactions of phosphate esters with other compounds. Cocaine undergoes metabolism by three major routes; one of these routes involves hydrolysis by liver and plasma cholinesterases to form ecgonine methyl ester. It has been suggested that cocaine users with serious complications tend to have lower plasma cholinesterase levels. Thus, it is possible that individuals with decreased plasma cholinesterase levels (such as resulting from organophosphate ester exposure) may be highly sensitive to cocaine (Cregler and Mark 1986; Hoffman et al. 1992). However, there are no experimental data to support this hypothesis.

A potentiation of neuropathy has been observed in studies involving administration of n-hexane or methyl *n*-butyl ketone with *O*-ethyl-*O*-4-nitrophenyl phenylphosphonothioate (EPN) (Abou-Donia 1983; Abou-Donia et al. 1985). Administration of each compound individually resulted in peripheral neuropathy. The peripheral neuropathy observed when n-hexane or methyl *n*-butyl ketone was administered simultaneously with EPN was more severe and had an earlier onset (Abou-Donia et al. 1985). The potential interactive effect of multiple exposures to different organophosphorus pesticides on delayed neuropathy has not been characterized (Chemiack 1988).

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2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to hydraulic fluids than will most persons exposed to the same level of hydraulic fluids in the environment. Reasons may include genetic makeup, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters may result in decreased function ofthe detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). 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.

No information was located regarding populations that may be unusually susceptible to toxic effects produced by mineral oil hydraulic fluids or polyalphaolefin hydraulic fluids.

Incomplete development of acetylcholinesterase systems and an immature liver may make infants (under 6 months) unusually susceptible to the cholinergic symptoms of organophosphate ester hydraulic fluids (Echobichon 1991; Evans 1986). This is supported by the Beck et al. (1977) study in cows (2 calves and >20 adults). A single oral exposure to Fyrquel 150 resulted in severe cholinergic effects, and the calves died after 13 days. Cows administered the same dose of Fyrquel exhibited equally severe cholinergic symptoms; however, the symptoms began to abate within 2 days, and lethality was not observed. Although the young appear to be more susceptible to the cholinergic symptoms of phosphate esters, they may be less sensitive to the delayed neuropathy (Abou-Donia and Lapadula 1990). Studies in chickens and rats have shown that neuropathic sensitivity gradually increases with age (Abou-Donia and Lapadula 1990; Johnson and Barnes 1970).

People with impaired liver function would be unusually susceptible to organophosphate ester exposure because of an impaired ability to metabolize organophosphate esters absorbed by the body. This population would primarily be composed of people suffering from liver diseases. Some groups have lower levels of plasma cholinesterase than the general population and are more susceptible to drugs such as succinylcholine which are metabolized by this enzyme. Some organophosphate esters can bind stoichiometrically to this

enzyme and inhibit its activity, possibly reducing plasma cholinesterase activity to a level where administration of succinylcholine would be dangerous. Low plasma cholinesterase levels have been seen in individuals with inherited abnormally low cholinesterase levels, long-distance runners, women during early pregnancy or using birth control pills, and individuals with advanced liver disease, chronic alcoholism, or malnutrition (Echobichon 1991; Evans 1986).

2.9 METHODS FOR REDUCING TOXIC EFFECTS

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

Studies designed to examine methods for reducing toxic effects of mineral oil, organophosphate ester, and polyalghaolefin hydraulic fluids in humans or animals were not located. Most hydraulic fluids are mixtures comprised of major and minor components whose presence may or may not be public information. Adverse health effects from exposure to mixtures can be caused by potent components which may represent only minor portions of the whole mixture and whose presence may not be common knowledge. This section discusses available information on methods for reducing toxic effects of major components of these classes of hydraulic fluids or of materials that may be expected to display similar toxicity and/or toxicokinetic properties. It should be noted that methods for reducing the toxic effects of the major component of the hydraulic fluid may not prevent the manifestations of toxic effects because the toxicity of the hydraulic fluid may be due to a minor component (such as organophosphate ester additives in mineral oil hydraulic fluids). Because the composition of a particular hydraulic fluid may vary greatly from other hydraulic fluids in the same class, it is suggested that health professionals attempt to obtain a label containing a list of all components of the hydraulic fluid of concern. Mineral oil hydraulic fluids frequently have organophosphate ester additives, so that in some cases-particularly in interfering with mechanism of action-the same strategies as for organophosphate esters might be applicable.

2. HEALTH EFFECTS

2.9.1 Reducing Peak Absorption Following Exposure

Mineral Oil Hydraulic Fluids. Mineral oil hydraulic fluids are expected to be poorly absorbed by the gastrointestinal tract (see Section 2.3). Although specific recommendations for treatment of acute intoxication from ingested mineral oil hydraulic fluids were not located, the removal of ingested petroleumderived hydrocarbons by intubation with a cuffed endotracheal tube followed by lavage has been suggested for cases where the patient is unconscious (Klein and Simon 1986). Warnings against the induction of vomiting have been made, because of the hazard of aspiration of the ingested fluids (Eade et al. 1974; Klein and Simon 1986). Food-grade or medicinal mineral oil (containing mostly aliphatic hydrocarbons) has cathartic properties (Brunton 1985). Administration of other cathartic agents (i.e., sorbitol) may result in a faster excretion rate, thus reducing gastrointestinal effects that may result from mineral oil hydraulic fluids passing through the gastrointestinal tract.

There is no available information on absorption of mineral oil hydraulic fluids following inhalation or dermal absorption. There are data suggesting that mineral oil aerosols are cleared from the lungs via alveolar macrophages. No specific methods to reduce absorption of dermally applied or inhaled mineral oil hydraulic fluids were located, but it is expected that removal of contaminated clothing and multiple washings of contaminated skin would reduce the dermal absorption of these materials.

Organophosphate Ester Hydraulic Fluids. Major components of organophosphate ester hydraulic fluids such as tricresyl phosphate isomers, isopropylated phenyl phosphates, and tributyl phosphate are readily absorbed through the gastrointestinal tract. These phosphate esters are slowly absorbed by the skin. No data on the absorption of inhaled tricresyl phosphate, isopropylated phenyl phosphate, or tributyl phosphate were located. No specific methods were located to reduce absorption of inhaled, ingested, or dermally applied organophosphate ester hydraulic fluids. Recommendations for the clinical treatment of organophosphorus insecticide poisonings, however, are likely applicable to poisonings with organophosphate ester hydraulic fluids. Recommended decontamination procedures to reduce absorption have included removal of contaminated clothing, washing of skin with alkaline soap that will remove and hydrolyze the-phosphate ester, washing of eyes with water or saline, and lavage of the stomach (Murphy 1986).

Polyalphaolefin Hydraulic Fluids. There is no information on the absorption of polyalphaolefin hydraulic fluids. Based on the physicochemical similarities between polyalphaolefins and mineral oils, it is likely that gastrointestinal absorption will be limited. No specific methods were located to reduce absorption of inhaled,

ingested, or dermally applied polyalphaolefin hydraulic fluids. Because certain polyalphaolefins are irritants following inhalation and dermal exposure (Kinkead et al. 1987b, 1992b; MacEwen and Vemot 1983) and the hazard of aspiration of the ingested fluids, it is questionable whether the induction of vomiting upon ingestion should be recommended as a method to reduce absorption. As with mineral oil hydraulic fluids, it is expected that removal of contaminated clothing and multiple washings of contaminated skin would reduce the dermal absorption of polyalphaolefin hydraulic fluids.

2.9.2 Reducing Body Burden

No specific methods were located to reduce the body burden of absorbed mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, or polyalphaolefin hydraulic fluids.

Absorbed hydrocarbons from mineral oil are likely to be preferentially distributed to the liver and fatty tissues and slowly metabolized to various types of lipids. Polyalphaolefins are expected to be similarly distributed and retained based on the similarities of the physical and chemical properties of polyalphaolefins and mineral oil.

Tricresyl phosphate isomers, a major component of some organophosphate ester hydraulic fluids, are widely distributed throughout the body with preferential uptake in fatty tissues, liver, and kidneys. The isomers are readily cleared without displaying a tendency to accumulate in tissues.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

Mineral Oil Hydraulic Fluids. No specific methods were located for interfering with the mechanism of action for toxic effects produced by mineral oil hydraulic fluids. Unstable alveoli and distal airways have been proposed as major factors in the respiratory symptoms that occur after the ingestion of other petroleumderived materials. Continuous positive airway pressure or continuous negative chest wall pressure, as well as the application of supplemental oxygen, have been recommended to counteract the resultant pneumonitis (Eade et al. 1974; Klein and Simon 1986).

Organophosphate Ester Hydraulic Fluids. Recommended procedures for interfering with the cholinergic toxic effects produced by organophosphoms insecticide poisonings are likely applicable to poisoning with organophosphate ester hydraulic fluids. Recommended treatments have included various regimens of

artificial respiration (if needed), atropine intravenous administration (to control muscarinic responses), and 2-pyridine aldoxime methiodide intravenous administration (to accelerate reactivation of phosphorylated acetylcholinesterase) (Ecobichon 1991; Murphy 1986). Administration of 2-pyridine aldoxime methiodide should be accomplished as soon as possible, but within 48 hours of organophosphate exposure (Ecobichon 1991). After this time, the phosphorylated acetylcholinesterase may become "aged" (i.e., irreversibly phosphorylated), and thus impossible to reactivate. The interference of the cholinergic toxicity of organophosphate esters is not necessarily expected to interfere with the development of organophosphate-induced delayed neurotoxicity (Ecobichon 1991). No methods to interfere with the development of OPIDN were located. It should be noted, however, that by the time symptoms of OPIDN appear, organophosphorus compounds and metabolites may have been cleared from the body (see Section 2.3).

Use of the muscle relaxant succinylcholine, which is metabolized by plasma cholinesterase, is contraindicated in cases of organophosphate poisoning (Giurini et al. 1986).

Polyalphaolefin Hydraulic Fluids. No specific methods were located for interfering with the mechanism of action for toxic effects produced by polyalphaolefin hydraulic fluids.

2.10 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 hydraulic fluids 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 hydraulic fluids.

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

2. HEALTH EFFECTS

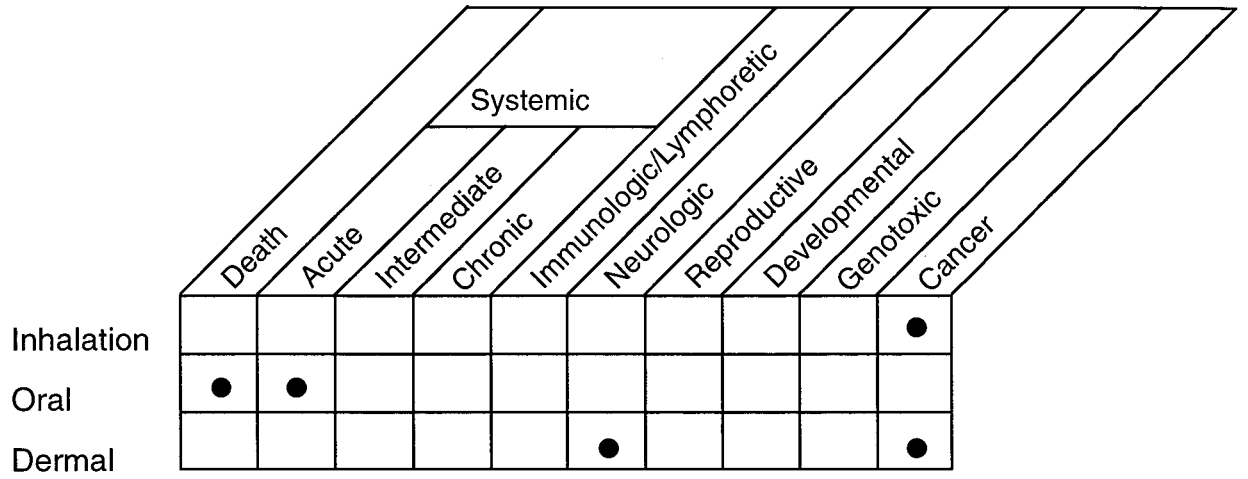
2.10.1 Existing Information on Health Effects of Hydraulic Fluids

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals from hydraulic fluids are summarized in Figures 2-8,2-9, and 2-10. The purpose of these figures is to illustrate the existing information concerning the health effects of hydraulic fluids. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

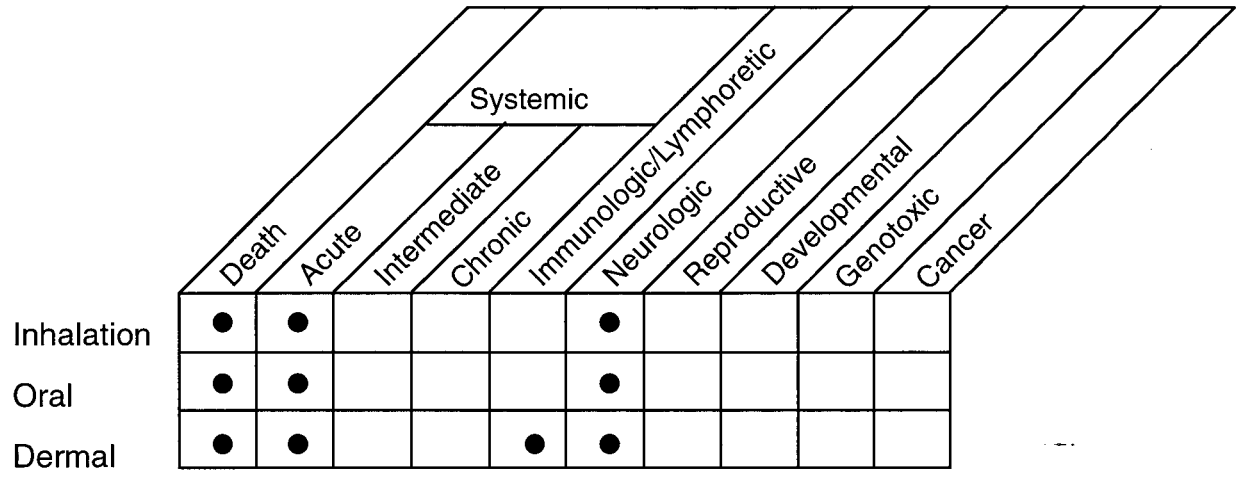
Mineral Oil Hydraulic Fluids. There is limited information on the toxicity of mineral oil hydraulic fluids in humans. A single case report of a child accidentally ingesting a single dose of automotive transmission fluid provides limited information on death and systemic effects. A case-control study provides some information on the carcinogenicity of mineral oil hydraulic fluids. The study population was exposed via inhalation and dermal routes. An occupational exposure study provides information on neurotoxicity following chronic dermal exposure. Information on the toxicity of mineral oil hydraulic fluids is limited to a series of inhalation, oral, and dermal acute-duration exposures. These studies provide information on death, systemic effects, and neurotoxicity by inhalation, oral, and dermal routes, and immunotoxicity following dermal exposure.

Organophosphate Ester Hydraulic Fluids. Information on human toxicity of organophosphate ester hydraulic fluids is very limited. Accidental poisonings (oral exposure) account for the majority of studies, though occupational exposure and dermal exposure is also reported. In animals, a number of organophosphate ester hydraulic fluids have been studied following inhalation exposure. These inhalation studies provide information on death, acute and intermediate systemic effects, possible information on immunotoxicity, neurotoxicity, and reproductive toxicity. Information on death, acute-, intermediate-, and chronic-duration systemic effects, immunological and lymphoreticular toxicity, neurotoxicity, reproductive toxicity, developmental toxicity, genotoxicity and cancer is available from oral exposure studies. Dermal exposure studies provide information on death, acute- and intermediate-duration systemic effects, immunotoxicity, neurotoxicity, reproductive toxicity, and developmental toxicity.

Figure 2-8. Existing Information on Health Effects of Mineral Oil Hydraulic Fluids



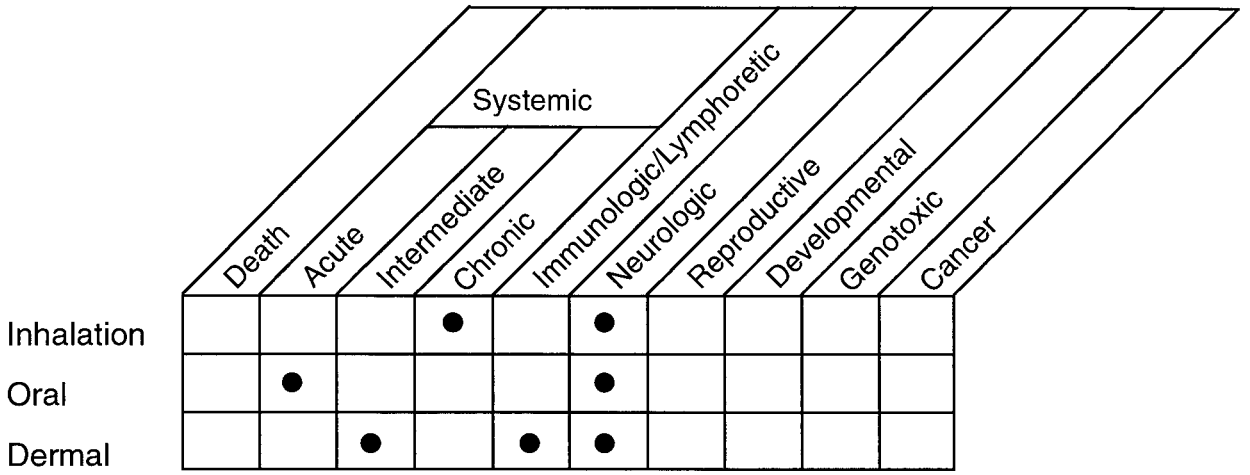
Human



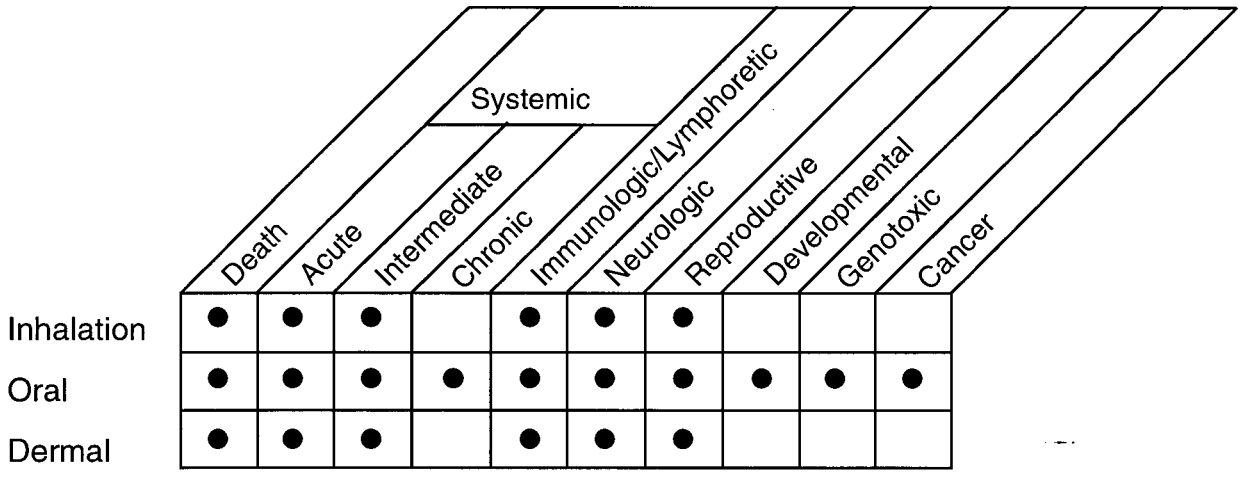
Animal

● Existing Studies

Figure 2-9. Existing Information on Health Effects of Organophosphate Ester Hydraulic Fluids



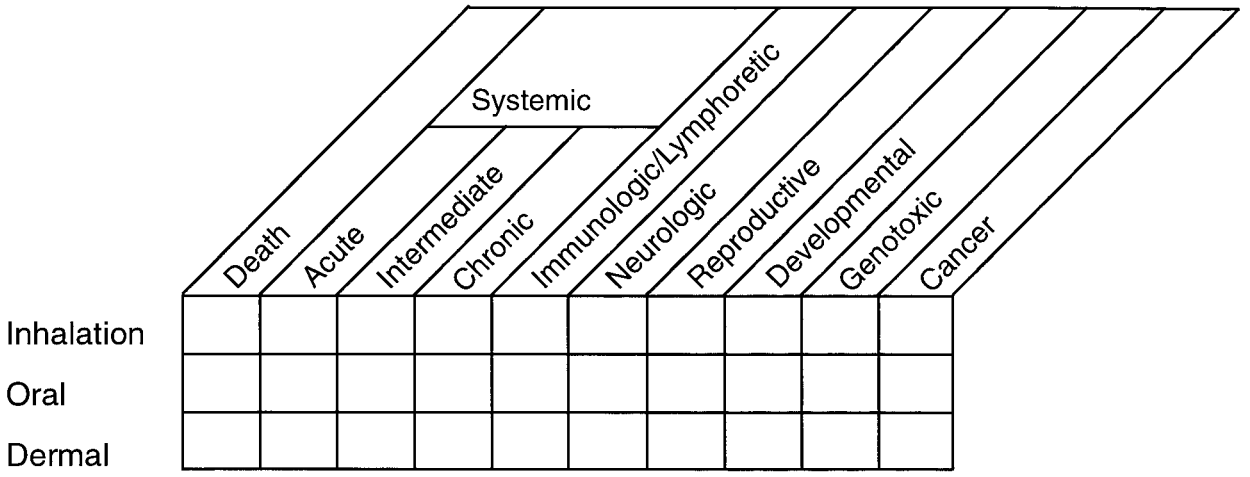
Human



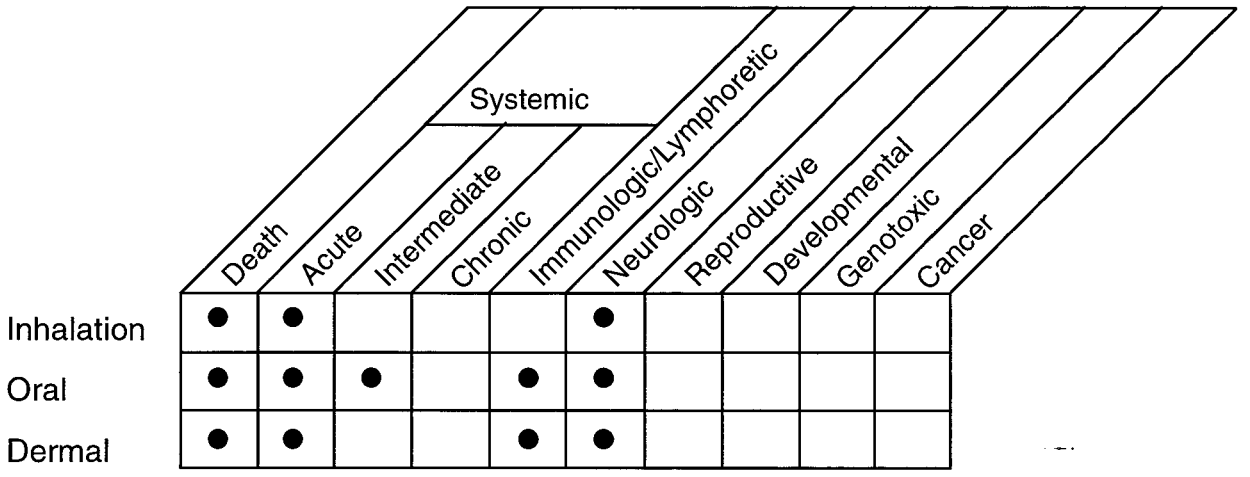
Animal

● Existing Studies

Figure 2-10. Existing Information on Health Effects of Polyalphaolefin Hydraulic Fluids



Human



Animal

● Existing Studies

2. HEALTH EFFECTS

No information was located on the toxicity of organophosphate ester hydraulic fluid breakdown products. Since these products may occur in the environment after disposal of organophosphate ester hydraulic fluids, this represents a potential data need in all categories.

Polyalphaolefin Hydraulic Fluids. No information on the toxicity of polyalphaolefin hydraulic fluids to humans was located.

A series of acute- and intermediate-duration inhalation, oral, and dermal exposure studies in animals provide information on death, systemic effects, neurological effects, and immunotoxicity following exposure to polyalphaolefin hydraulic fluids.

2.10.2 Identification of Data Needs

Acute-Duration Exposure.

Mineral Oil Hydraulic Fluids. There is limited information on the acute toxicity of mineral oil hydraulic fluids to humans. A single case report of a child accidentally ingesting automotive transmission fluid reported respiratory and gastrointestinal effects (Perrot and Palmer 1992).

There is also limited animal data. A series of acute inhalation, oral, and dermal lethality studies monitored death and body weight gain in rats exposed to Sunsafe F, Quintolubric 9583OW, Houghto-Safe 5047F, or Pyroguard A-443 mineral oil hydraulic fluids (Kinkead et al. 1988, 1989a) or mineral oil hydraulic fluids meeting military specifications of MIL-H-5606 (Kinkead et al. 1985). The dermal and ocular irritancy of these fluids has also been tested (Kinkead et al. 1985, 1988, 1989a). These lethality studies are not adequate for the derivation of acute inhalation or oral MRLs. No acute-duration studies performing complete histopathological examinations or repeated exposure studies that identify target organs were located. These studies would be useful in determining the health risks of individuals acutely exposed to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. Human studies of exposure to organophosphates are primarily those of acute, accidental poisonings with tricresyl phosphate (Goldstein et al. 1988; Senayanake and Jeyaratnam 1981; Srivastava et al. 1990).

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In rats, studies of the acute toxicity of inhaled Durad MP280 and Fyrquel 220 (Gaworski et al. 1986), examined respiratory, hepatic, and renal end points and found no effects. In rabbits, acute inhalation exposure to Cellulube 220 caused respiratory and gastrointestinal problems (Carpenter et al. 1959). Mice and rabbits exhibited acute neurotoxicity with exposure to triphenyl phosphate and Cellulube 220 (Carpenter et al. 1959; Sutton et al. 1960). Acute-duration oral exposure studies were located for rats, mice, guinea pigs, rabbits, hens, goats, and cows exposed to Durad 220B (FMC 1990a), Durad 550B (FMC 1992a), Durad 110 (FMC 1990a), Durad 300 (FMC 1990a), Cellulube 220 (Dollahite and Pierce 1969; Carpenter et al. 1959), Reofos 65 (Mortensen and Ladefoged 1992), Pydraul 50E (Ciba-Geigy 1973), Fyrquel EHC (Mortensen and Ladefoged 1992), Fyrquel 220 (FMC 1977a), Skydrol 500B-4 (Monsanto 1987d), Skydrol LD-4 (Monsanto 1987c), Fyrquel 150 (Beck et al. 1977), ethylhexyldiphenyl phosphate (Noda et al. 1984), butylated triphenyl phosphate (Latendresse et al. 1994), dibutylphenyl phosphate (Carrington et al. 1989), isopropyltriphenyl phosphate (Sprague et al. 1984), Santicizer 141048 (Robinson et al. 1986), tributoxyethyl phosphate (Carrington et al. 1989), triphenyl phosphate (Sutton et al. 1960), and tributyl phosphate (Healy et al. 1995; Johannsen et al. 1977).

Neurotoxic end points, especially acetylcholinesterase and related enzymes, were the most heavily studied, but other studies have expanded the toxicity literature to include developmental, immunological, and systemic effects. The acute dermal toxicity of Fyrquel 220 and Durad MP280 (Gaworski et al. 1986; Kinkead et al. 1992a, 1992d, 1992e), Durad 220B, Durad 110, and Durad 300 (FMC 1990a), Durad 125 (FMC 1991b), cyclotriphosphazene (Kinkead et al. 1992c; MacEwen and Vemot 1985), and Durad 550B (FMC 1992c) has been tested in rats and rabbits. These studies were designed to examine dermal and/or ocular irritancy or to assess neurotoxicity. Because the inhalation and oral exposure studies examined a limited number of end points, MRLs could not be derived. EPA has been negotiating an Enforceable Consent Agreement with the manufacturers of aryl phosphates and in reviewing the needs for testing, acute testing is not identified (EPA 1994).

Polyalphaolefin Hydraulic Fluids. No acute exposure human studies were located.

There is limited information on the acute toxicity of polyalphaolefin hydraulic fluids to animals. Several single 4-hour exposure studies identified the respiratory tract as a target of toxicity following exposure to polyalphaolefin hydraulic fluids designated as B85-174 (Kinkead et al. 1987b), MIL-H-83282LT (Kinkead et al. 1992b), or DTNSRDC N501 (MacEwen and Vemot 1983). Acute inhalation, oral, and dermal lethality studies on polyalphaolefin hydraulic fluids designated as DTNSRDC N448, N501, N5 17, N5 18, N525, or

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N527 (MacEwen and Vemot 1983) or a polyalphaolefin hydraulic fluid meeting military specifications of MIL-H-83282 (Kinkead et al. 1985) provide evidence that polyalphaolefin hydraulic fluids were not very lethal and did not affect body weight gain. Dermal and ocular irritancy were also assessed using polyalphaolefin hydraulic fluids designated as DTNSRDC N448, N501, N5 17, N5 18, N525, or N527 (MacEwen and Vemot 1983), MIL-H-83282LT (Kinkead et al. 1992b), B85-174 (Kinkead et al. 1987b), or meeting military specifications of MIL-H-83282 (Kinkead et al. 1985). The DTNSRDC N501 was a mild skin irritant and MIL-H-83282LT was a eye irritant. Based on these animal data, the targets of toxicity of polyalphaolefin hydraulic fluids cannot be identified. Repeated exposure and studies conducting complete histological examinations would be useful in assessing the risk of individuals exposed to polyalphaolefin hydraulic fluids for acute durations.

Intermediate-Duration Exposure.

Mineral Oil Hydraulic Fluids. No intermediate exposure human studies were located.

Two studies on intermediate-duration exposure to mineral oil hydraulic fluids are available: a single oral exposure rat study to MIL-H-5606 (Mattie et al. 1993), and an inhalation-exposure study in rats to Houghto-Safe 5047F (Kinkead et el. 1991). Because no other intermediate-duration studies were located, no inhalation or oral intermediate MRLs were derived. Inhalation, oral, and dermal systemic toxicity studies examining a number of end points would be useful in identifying the targets of toxicity of mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. Four human exposure studies were located. In one study, no change in hematological parameters was observed in workers dermally exposed to organophosphate ester hydraulic fluids for an intermediate duration (Baldridge et al. 1959). The application of patches containing Skydrol500B-4 resulted in erythema in individuals exposed for an intermediate duration (Monsanto 1980). A woman developed an allergic reaction to triphenyl phosphate found in the frames of her glasses (Carlson et al. 1986) and a man also became hypersensitive to organophosphates found in a glue he was using (Camaras and Serra-Baldrich 1992).

The toxicity of inhaled triaryl phosphates (triaryl phosphate-mixture), Fyrquel 220, Durad MP280, and cyclotriphosphazene has been well studied in rats, rabbits, and hamsters. These studies suggest that Fyrquel 220 (Gaworski et al. 1986; MacEwen and Vemot 1983), Durad MP280 (Gaworski et al. 1986; MacEwen and Vemot 1983), cyclotriphosphazene (Kinkead et al. 1989a, 1990), and Cellulube 220 (Carpenter et al.

1959; Siegel et al. 1965) are not potent systemic toxicants. No further inhalation exposure studies are needed for these organophosphate ester hydraulic fluids. Although there is a reasonable body of data for intermediate oral exposure to organophosphate esters, EPA and the aryl phosphate industry are planning additional testing (EPA 1994). The National Toxicology study, published in 1994, has helped to define oral, systemic end points for exposure to tricresyl phosphate. Adrenal, liver and body weight changes are reported in rats and mice. Endocrine effects are further delineated for rats exposed to TCP and butylated triphenyl phosphate (Latendresse et al. 1994a, 1994b; Oishi et al. 1982). Following exposure to low doses of Pydraul 90E, no evidence of systemic toxicity was observed in rats (Monsanto 1979) and no changes in body weight gain were observed in hens exposed to Durad 110 (FMC 1986). As a broad range of systemic end points become defined, it would be useful to have additional testing of systemic effects. A number of studies on organophosphorus ester hydraulic fluids suggest that neurological effects may be the most sensitive end point of toxicity. Because of limitations in the neurotoxicity database, inhalation and oral intermediate-duration MRLs were not derived. Information is available on the intermediate-duration dermal toxicity in rabbits of cyclotriphosphazene (Kinkead et al. 1989c, 1990), Fyrquel220 (MacEwen and Vemot 1983), and Cellulube 220 (Carpenter et al. 1959). No further systemic toxicity studies on the dermal toxicity of cyclotriphosphazene and Fyrquel 220 are needed. (Cellulube 220 is no longer in production.) Studies on other organophosphate ester hydraulic fluid components might be useful for assessing the potential for human toxicity following intermediate-duration exposure.

Polyalphaolefin Hydraulic Fluids. No intermediate exposure human studies were located.

Information on polyalphaolefin hydraulic fluids is limited to a single study in rats orally exposed to MIL-H-83282 and MIL-H-83282LT (Mattie et al. 1993). Intermediate-duration inhalation or oral MRLs could not be derived based on a single study. Significant toxicity was not observed. Systemic toxicity studies in which animals were exposed via inhalation and dermal routes would be useful in identifying the end points of toxicity for humans living at or near hazardous waste sites and exposed for intermediate-durations.

Chronic-Duration Exposure and Cancer.

Mineral Oil Hydraulic Fluids. No human or animal studies involving inhalation, oral, or dermal chronicduration exposure were located. Because no chronic-duration studies were located, no inhalation or oral chronic MRLs were derived. Inhalation, oral, and dermal systemic toxicity studies examining a number of end points would be useful in identifying the targets of toxicity of mineral oil hydraulic fluids.

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One human carcinogenicity exposure study was located. This study did not find convincing associations between exposure to hydraulic fluid and the incidence of cancer at a specific site (Siemiatycki et al. 1987a). As discussed in Section 2.2.1.8, there are a number of limitations to this study. An animal carcinogenicity study or well-controlled cohort retrospective or prospective study would be useful for determining the carcinogenic potential of mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No chronic exposure human studies were located.

Chronic animal studies of organophosphates are few in number, but those that do exist provide a useful base from which to draw toxicological insight. In rats and mice exposed orally to tricresyl phosphate for 2 years, endocrine effects were found in a dose-response pattern and hepatic effects were found. Ovarian interstitial hyperplasia was also observed but was not dose related. No chronic-duration MRLs could be derived because of the limited number of studies. Tricresyl phosphate, a component of certain hydraulic fluids, produced no evidence of carcinogenic activity in assays with rats and mice (NTP 1994). However, another component, tributyl phosphate, was associated with an increased incidence of bladder tumors in rats and mice (FMC 1994a, 1994b).

Polyalphaolefin Hydraulic Fluids. Because no chronic-duration human or animal inhalation, oral, or dermal exposure studies using polyalphaolefin hydraulic fluids were located, chronic-duration inhalation or oral MRLs could not be derived. Systemic toxicity studies in which animals were exposed via inhalation, oral, and dermal routes would be useful in identifying the end points of toxicity for humans living at or near hazardous waste sites and exposed for chronic durations. Further carcinogenicity studies on individual organophosphate ester components of hydraulic fluids may be useful.

No information on the carcinogenic potential of polyalphaolefin hydraulic fluids was located. Studies designed to assess carcinogenicity in animals exposed via inhalation, oral, and dermal routes or a well controlled cohort retrospective or prospective study would be useful for determining the carcinogenic potential of polyalphaolefin hydraulic fluids.

Genotoxicity.

Mineral Oil Hydraulic Fluids and Polyalphaolefin Hydraulic Fluids. No studies were located regarding genotoxicity after inhalation, oral, or dermal exposure to mineral oil hydraulic fluids or polyalphaolefin.

hydraulic fluids. No studies were located regarding genotoxicity of mineral oil hydraulic fluids or polyalphaolefin hydraulic fluids in *in vitro* assays. Studies that address the genotoxicity of members of these classes of hydraulic fluids would be helpful.

Organophosphate Ester Hydraulic Fluids. *In vivo* genotoxicity assays have been conducted for two organophosphate ester hydraulic fluids. Results have generally been negative. The *in vivo* genotoxicity of Reofos 50 and Reolube HYD46 has been tested in Chinese hamsters (Ciba-Geigy 1983b, 1984a, 1984b). Durad 550B (FMC 1992b), Reofos 95 (Ciba-Geigy 1978a), Reolube HYD46 (Ciba-Geigy 1983a, 1984a), Reofos 50 (Ciba-Geigy 1978b, 1984b), Skydrol500B-4 (Monsanto 1988a), and Skydrol LD-4 (Monsanto 1988b) have been tested for *in vitro* genotoxicity using gene mutation, DNA damage, and/or chromosomal aberrations. In EPA's Notice of Proposed Test Rule for aryl phosphates there is no mention of genotoxic testing (EPA 1992), nor is there an identified need for genotoxic testing in the 1994 EPA Testing Consent Order (EPA 1994).

Reproductive Toxicity.

Mineral Oil Hydraulic Fluids and Polyalphaolefin Hydraulic Fluids. No studies were located regarding reproductive toxicity after exposure by any route to mineral oil or polyalphaolefin hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. Rats and mice were tested with oral exposure to certain components of organophosphate ester hydraulic fluids, generally for subchronic periods, and effects were reported for both males and females. Females showed ovarian interstitial hypertrophy, increased ovarian weights, and decreased fertility after exposure to tricresyl phosphate (Latendresse et al. 1994a, 1994b; NTP 1994). Males exhibited abnormal sperm, necrosis of seminiferous tubules, and reduced testes weights after exposure to tricresyl phosphate (Carlton et al. 1987; Latendresse et al. 1994a, 1994b; NTP 1994). Reproductive toxicity is an area of concern, and further reproductive toxicity testing on individual components of organophosphate ester hydraulic fluids would be useful.

Developmental Toxicity.

Mineral Oil Hydraulic Fluids and Polyalphaolefin Hydraulic Fluids. The developmental toxicity data base is generally inadequate. No studies were located regarding developmental toxicity after exposure by any route to mineral oil hydraulic fluids or polyalphaolefin hydraulic fluids.

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Organophosphate Ester Hydraulic Fluids. No studies concerning developmental effects of organophosphate ester hydraulic fluids in humans were located; among the limited number of studies that report organophosphate ester developmental toxicity are reports of reduced litter size, pup survivability and pup weights in rats with tricresyl phosphate and dibutyl phenyl phosphate (Carlton et al. 1987; Healy et al. 1991). Teratogenicity was not observed. The database also has two observations of developmental effects in cows that were probably environmentally exposed to organophosphate ester hydraulic fluids (Beck et al. 1977; Julian et al. 1976). Further developmental toxicity testing may be warranted.

Immunotoxicity.

Mineral Oil Hydraulic Fluids. No information was located regarding immunological effects in humans after inhalation, oral, or dermal exposure to mineral oil hydraulic fluids. Data from animal testing of limited immunological end points suggest that the immunological system may not be a sensitive target for certain mineral oil hydraulic fluids. In guinea pig skin sensitization assays, four of five tested mineral oil hydraulic fluids were inactive as skin sensitization agents, and the remaining fluid only showed weak activity (Kinkead et al. 1985, 1987a, 1988). Testing of other mineral oil hydraulic fluids using an immunological test battery in animals by several routes of exposure would help to determine if the immunologic system is a target of mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. No dermal sensitization reactions were observed in a study of human subjects exposed dermally to Skydrol 500B-4 (Monsanto 1980) or in a study of guinea pigs exposed to a cyclotriphosphazene-based hydraulic fluid (Kinkead et al. 1992c; MacEwen and Vemot 1985). Two case reports indicate dermal sensitization from eyeglass frames and glue (Carlsen et al. 1986; Camarasa and Serra-Baldrich 1992). No histological alterations were observed in the thymus of rats exposed to aerosols of cyclotriphosphazene for 21 days (Kinkead et al. 1989a, 1990). Thymus weight decreases (both absolute and relative to body weight) were observed, without histological alterations, in rabbits exposed dermally to cyclotriphosphazene (Kinkead et al. 1989c, 1990). Additional testing of other organophosphate ester hydraulic fluids would provide support for the hypothesis suggested by the limited available data that skin sensitization may not be a concern with dermal exposure to organophosphate ester hydraulic fluids. Testing of other organophosphate ester hydraulic fluids for additional immunological end points in animals would help to determine if the immunologic system is a target of these materials.

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Polyalphaolefin Hydraulic Fluids. No data were located regarding immunological effects in humans after exposure to polyalphaolefin hydraulic fluids. Results from guinea pig skin sensitization assays indicated that two of nine tested polyalphaolefin hydraulic fluids were skin sensitizers (Kinkead et al. 1985, 1992b; MacEwen and Vemot 1983). Data from oral administration is limited to histological examination of immunological tissues where no effect was found (Mattie et al. 1993). Examination of additional immunological end points in animals after oral, inhalation, and dermal exposure to polyalphaolefin hydraulic fluids would help to determine the likelihood of immunologic effects occurring in humans exposed to environmental media contaminated with these materials.

Neurotoxicity.

Mineral Oil Hydraulic Fluids. Reports of neurological effects in humans or animals are restricted to a single case report of neuropathy in a man who was heavily exposed to mineral oil hydraulic fluids by occupational dermal contact (Jarvholm et al. 1986) and a report of subtle electromyographical effects in four of eight examined men who were less heavily exposed by occupational dermal contact (Jkvholm et al. 1986). However, an association between human exposure to mineral oil hydraulic fluids and neurological effects is uncertain, due to the lack of corroborative case reports and epidemiological data and the lack of studies demonstrating neurological effects in animals after exposure to mineral oil hydraulic fluids. The presence of organophosphate ester additives in many mineral oil hydraulic fluids raises some concern regarding neurotoxicity, but levels of these additives are normally low. Acute inhalation, oral or dermal testing of additional fluids for organophosphate-induced delayed neuropathy (OPJDN) in sensitive species (e.g., cats or chickens) may provide useful information to ascertain the neurological hazard presented by mineral oil hydraulic fluids. No information was located regarding neurological effects in humans or animals after intermediate to chronic exposure to mineral oil hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. Neurotoxicity is a concern from acute dermal, inhalation, or oral exposure to organophosphate ester hydraulic fluids because of the well-established susceptibility of humans to the cholinergic and delayed neuropathic properties of certain organophosphate este compounds such as TOCP. Sufficient acute oral testing of organophosphate hydraulic fluids in chickens has been conducted to conclude that there is a wide range in the ability of organophosphate ester fluids to produce adverse neurological effects. Certain fluids (e.g., Durad 220B and Durad 125), however, have not been tested for neurotoxicity in sensitive animal species. Acute testing of these additional organophosphate hydraulic fluids for neurotoxicity in chickens will provide useful information regarding their potential to produce acute

neurological effects. Dermal or inhalation testing in cats (another sensitive species to OPIDN) may provide additional information regarding the hazard from these expected routes of certain occupational exposures. It is unknown if long-term, low-dose exposures to organophosphate ester hydraulic fluids will produce neurological effects. Experiments with hens, however, suggested that with longer exposure periods, lower doses of Durad 110 produced increased incidences of ataxia and nerve damage. A LOAEL of 1,333 mg/kg/day was observed with a 2%day oral exposure, compared with a LOAEL of 90 mg/kg/day with 90 days of exposure (FMC 1986). Additional animal experiments with other organophosphate ester hydraulic fluids are needed to assess the neurological hazard presented by intermediate to chronic exposure.

Polyalphaolefin Hydraulic Fluids. Several polyalphaolefin hydraulic fluids have been tested for clinical signs of OPIDN in chickens after acute gavage exposure, but adverse effects were not seen (Kinkead et al. 1985, 1992b). As with mineral oil hydraulic fluids, the possible presence of organophosphate ester additives in these fluids may raise some concern regarding neurotoxicity, but levels would normally be expected to be low. Acute oral or dermal testing of additional fluids for OPIDN in sensitive species may be useful to further ascertain the neurological hazard presented by polyalphaolefin hydraulic fluids. No information was located regarding neurological effects in humans or animals after intermediate to chronic exposure to polyalphaolefin hydraulic fluids.

Epidemiological and Human Dosimetry Studies.

Mineral Oil Hydraulic Fluids. Two human studies involving exposure to mineral oil hydraulic fluids were located. One was a case report of a child who accidentally ingested a lethal dose of automotive transmission fluid (Perrot and Palmer 1992). The other is an occupational exposure in which workers were dermally exposed to mineral oil hydraulic fluids (Jarvholm et al. 1986). Both of these studies are limited because only a small number of end points were examined and there is no accurate reporting of dose levels. Because mineral oil hydraulic fluids are widely used, the potential for human exposure is great. The identified human studies and the animal studies did not identify the primary target of toxicity for mineral oil hydraulic fluids. Epidemiology studies of workers (including auto mechanics exposed to transmission fluids) exposed to mineral oil hydraulic fluids would be useful in identifying targets of toxicity.

Organophosphate Ester Hydraulic Fluids. Two human exposure studies were identified. In these studies, individuals were dermally exposed to organophosphate ester hydraulic fluids for an intermediate duration (Baldridge et al. 1959; Monsanto 1980). In the Baldridge et al. (1959) study, no hematological or

neurological effects were observed. The Monsanto (1980) study was designed to assess dermal irritation and sensitization. Organophosphate ester hydraulic fluids are fire-resistant hydraulic fluids used in the hydraulic systems of aircraft; thus, there is a potential for occupational exposure. The animal data suggest that the most sensitive target of toxicity is the neurological system. Studies designed to monitor acetylcholinesterase inhibition, particularly in the workplace, would be useful in establishing dose-response relationships.

Polyalphaolefin Hydraulic Fluids. No human studies for polyalphaolefin hydraulic fluids were located. Polyalphaolefin hydraulic fluids are used in U.S. military aircraft hydraulic systems; thus, there is a potential for occupational exposure. Animal studies were insufficient for determining the primary targets of toxicity. Epidemiology studies examining a number of end points would be useful for identifying targets of toxicity.

Biomarkers of Exposure and Effect.

Exposure.

Mineral Oil Hydraulic Fluids and Polyalphaolefin Hydraulic Fluids. The data bases regarding the toxicity of mineral oil and polyalphaolefin hydraulic fluids are very limited. Further toxicity testing may elucidate biomarkers of exposure for these classes of hydraulic fluids.

Organophosphate Ester Hydraulic Fluids. Interpretation of the biomarkers of exposure to organophosphate ester hydraulic fluids is complicated by the diversity of composition among the hydraulic fluids in this class. Erythrocyte acetylcholinesterase activity is a good biomarker of exposure to certain organophosphates (e.g., insecticides), but results are inconsistent with organophosphate components of hydraulic fluids. A biomarker of exposure to any component of a hydraulic fluid would serve as a biomarker of exposure to the hydraulic fluid itself.

Effect.

Mineral Oil Hydraulic Fluids and Polyalphaolefin Hydraulic Fluids. The data bases of the toxicity of mineral oil and polyalphaolefin hydraulic fluids are very limited. Further toxicity testing may elucidate biomarkers of effect for these classes of hydraulic fluids.

2. HEALTH EFFECTS

Organophosphate Ester Hydraulic Fluids. The biomarkers of effects after exposure to organophosphate ester hydraulic fluids are well established in cases of delayed neuropathy (clinical signs of peripheral neuropathy). Further study would be helpful to determine whether certain effects (such as diarrhea after oral exposure) are due to direct action of the toxic agent on the target organ or to inhibition of acetylcholinesterase at the acetylcholine nerve receptor site on the organ.

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetics database is inadequate. Very limited data were located regarding relative rates of absorption, distribution, metabolism, and excretion after exposure to mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, or polyalphaolefin hydraulic fluids. The extent of located pertinent data is: a study describing the *in vivo* absorption and excretion of cyclotriphosphazene (rates were not quantified), the *in vivo* metabolism of Reolube HYD46 to cyclic and mono-hydroxylated metabolites (rate was not quantified), and observations concerning the ***in vitro*** absorption of components of Reolube HYD46 and Reofos 50 (Yang et al. 1990). There are data on the toxicokinetics of some of the major components of these classes of hydraulic fluids. Data on these components does not obviate the need for data on the hydraulic fluids, per se, because many of the fluids are complex mixtures of chemicals that may include some components which may not share toxicokinetic properties with the major components. No data were located regarding differences in absorption, distribution, metabolism, or excretion with respect to time or dose.

Comparative Toxicokinetics. The toxicokinetics database is wholly inadequate with respect to comparing toxicokinetics across species, largely because of the dearth of baseline data regarding absorption, distribution, metabolism, and excretion in any species after exposure to mineral oil hydraulic fluids, organophosphate ester hydraulic fluids, or polyalphaolefin hydraulic fluids. Also, no studies were located on the toxicokinetic properties of hydraulic fluids in humans.

Methods for Reducing Toxic Effects.

Mineral Oil Hydraulic Fluids. Aside from the possibility of the development of pneumonitis.following the aspiration of ingested mineral oil hydraulic fluid, little is known regarding the toxicity of these materials. Additional animal studies to identify the possible toxic effects of exposure to these materials may provide information relevant to the investigation of methods for reducing the toxic effects.

2. HEALTH EFFECTS

Organophosphate Ester Hydraulic Fluids. There are no established methods for reducing absorption of organophosphate esters. Studies in animals designed to identify agents that could inhibit or delay the absorption of organophosphate esters may provide valuable information for the preventive treatment of acute neurotoxic effects produced by some organophosphate ester hydraulic fluids. The mechanism of the acute cholinergic toxicity of organophosphorus esters is well known, as are methods to interfere with it. Identification of chemicals that reactivate "irreversibly" inhibited acetylcholinesterase would be valuable in the treatment of acute poisoning by organophosphorus esters. In contrast, the mechanism of OPIDN is poorly understood. Additional studies on the mechanism of OPIDN may provide information relevant to the identification of chemicals that interfere with a requisite step in its development.

Polyalphaolefin Hydraulic Fluids. Aside from the acute lethality of inhalation exposure to certain polyalphaolefin hydraulic fluids, little is known regarding the toxic effects produced by these materials. Additional animal studies to identify the possible toxic effects of exposure to these materials may provide information relevant to the investigation of methods for reducing the toxic effects.

2.10.3 Ongoing Studies

Dr. D.R. Mattie and colleagues at the Wright-Patterson Air Force Base Armstrong Laboratory are involved in ongoing evaluations of the comparative toxicity of various hydraulic fluids used by the U.S. Air Force. Results from subchronic toxicity studies with rats orally exposed to mineral oil and polyalphaolefin hydraulic fluids are being prepared for publication. Under the Toxic Substances Control Act, EPA and aryl phosphate industry representatives are negotiating a test program to cover toxicological gaps in our present knowledge and potential environmental exposure to aryl phosphates. The EPA has published a proposed test rule (EPA 1992b) for testing aryl phosphate base stocks. The proposed tests include: chronic exposure neurotoxicity in the hen, two-generation reproduction and fertility effects, subchronic mammalian toxicity, and developmental toxicity. Since this proposed rule was published in January 1992, the comment period has closed, and EPA is considering what stocks to test, what tests to proceed with, and how to implement any testing program.