3. HEALTH EFFECTS

3.1 INTRODUCTION

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

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

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

3.2.1 Inhalation Exposure

Studies of the inhalation toxicity of cresols have not been adequately detailed. The exposures involved mixtures of vapors and aerosols that were not characterized sufficiently to estimate exposure levels reliably. Furthermore, methods for evaluating the toxicological end points were not adequately described. In addition, it is very likely that dermal exposure, and thus dermal absorption, also occurred. Therefore, no LSE table or figure containing levels of significant exposure was constructed for this route. Nevertheless, certain general conclusions can be drawn from the reports regarding the toxic potential of inhaled cresols. These are discussed below.

3.2.1.1 Death

No studies were located regarding death in humans following inhalation exposure to cresols.

Cresols may be lethal to animals when inhaled (Campbell 1941; Uzhdavini et al. 1972). The inhalation exposure levels and durations that kill animals have not been reliably documented. Lethality has been reported in mice exposed to approximately 178 mg/m^3 of *o*-cresol aerosol for an unspecified acute duration, suggesting that the minimal lethal exposure level for cresol aerosols may be <178 mg/m^3 (Uzhdavini et al. 1972). For longer-term exposure, the minimal lethal level may exceed 50 mg/m^3, since exposure to this concentration of *o*-cresol for 1 month had no effect on mouse mortality (Uzhdavini et al.

1972). Clinical signs that preceded death in acute experiments included irritation of mucous membranes and neuromuscular excitation that progressed from tremors to clonic convulsions.

3.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, hematological, musculoskeletal, or dermal effects in humans or animals following inhalation exposure to cresols.

Respiratory Effects. When inhaled as a concentrated aerosol, *o*-cresol is a respiratory irritant in humans; however, the minimal exposure level and duration associated with irritation have not been reliably documented. Following brief exposures to 6 mg/m^3, 8 out of 10 subjects complained of mucosal irritation symptoms including dryness, nasal constriction, and throat irritation (Uzhdavini et al. 1972).

Signs of respiratory irritation have been reported in animals acutely exposed to cresol vapors and aerosols, although the levels associated with irritation have not been reliably documented (Campbell 1941; Uzhdavini et al. 1972). Mucosal irritation, as shown by parotid gland secretions, occurred in cats during 30-minute exposures to 5–9 mg/m^3 of *o*-cresol (Uzhdavini et al. 1972). An assortment of respiratory effects, including inflammation and irritation of the upper respiratory tract, pulmonary edema, and hemorrhage and perivascular sclerosis in the lungs were seen in animals exposed to 9–50 mg/m^3 of *o*-cresol 2–6 hours/day for ≥1 month (Uzhdavini et al. 1972).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following inhalation exposure to cresols.

Heart muscle degeneration was reported in mice exposed to 50 mg/m^3 of *o*-cresol 2 hours/day for 1 month (Uzhdavini et al. 1972). Mice were probably exposed to an aerosol. Exposure levels were not reliably documented.

Hepatic Effects. No studies were located regarding hepatic effects in humans following inhalation exposure to cresols.

Fatty degeneration and centrilobular necrosis were observed in the livers of mice that died following acute exposure to *o*-cresol; the mean lethal concentration was 178 mg/m^3. Exposure to 9 mg/m^3 for

4 months interfered with liver function in rats, as shown by increased susceptibility to hexanol narcosis (Uzhdavini et al. 1972).

Renal Effects. No studies were located regarding renal effects in humans following inhalation exposure to cresols.

Blood was found in the urine of mice acutely exposed to *o*-cresol; the mean lethal concentration was 178 mg/m^3 (Uzhdavini et al. 1972). Necropsy and histopathologic examination of the mice that died following exposure revealed edema and swelling of the glomeruli, degeneration of the tubular epithelium, and perivascular hemorrhage.

Ocular Effects. No studies were located regarding ocular effects in humans following inhalation exposure to cresols.

Eye irritation was noted in mice briefly exposed to highly concentrated cresylic acid (a mixture of cresol isomers and other phenolic solvents that boils above 204 °C) vapors; however, the exact exposure concentrations associated with irritation were not documented (Campbell 1941).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals following inhalation exposure to cresols.

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans following inhalation exposure to cresols.

Neurologic effects in animals acutely exposed to cresol aerosols have been reported (Uzhdavini et al. 1972). The effects include mild nervous excitation, muscle twitching accompanied by general fatigue, and clonic convulsions. The exposure concentrations associated with these effects have not been reliably documented; however, they may occur at levels approximating 178 mg/m^3 during a single exposure. Prolonged exposure (2 hours/day for 1 month) to a lower concentration of *o*-cresol aerosol (50 mg/m^3) reportedly produced degeneration of nerve cells and glial elements in mice (Uzhdavini et al. 1972). The

severity of these changes was not discussed, however, and no further details were provided. The exposure concentration associated with this effect was not reliably documented.

No information was located regarding the following effects of cresols in humans following inhalation exposure:

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

3.2.2 Oral Exposure

3.2.2.1 Death

Ingestion of cresols can be fatal to humans. Fatalities were described in several case reports involving ingestion of cresol-containing disinfectants. A 37-year-old woman died 4 days after swallowing about 250 mL of a disinfectant described as 50% cresols in a mixture of linseed oil, potassium hydroxide, and water. Death was caused by acute intravascular hemolysis, which resulted in multiple thrombosis and renal failure (Chan et al. 1971). The lethal dose was roughly 2 g/kg of cresols (only about one-half of which was actually absorbed). The same report described the case of a woman who recovered after drinking a smaller amount of the same disinfectant (approximately 100 mL). The urine of both women contained glucuronides of cresol metabolism. A woman who swallowed between 500 and 750 mL of a concentrated cresol mixture died from cardiac arrest 26 hours later (Labram and Gervais 1968). Among the 52 cases of cresol poisoning reported by Isaacs (1922), two patients died, both within 0.5 hours of drinking a disinfectant purported to contain 25–50% cresols. Similarly, Monma-Ohtaki et al. (2002) reported that ingestion of a large volume of a saponated cresol solution caused the death of a man in about 15 minutes. A woman who drank a disinfectant suspected of containing cresols died 5 days later (Dellal 1931). There was little corrosion in the throat so it is probable that not much disinfectant was swallowed. The cause of death was thought to be acute hemorrhagic degeneration of the pancreas, which may or may not have been related to cresol consumption. Bruce et al. (1976) also described two cases of ingestion of cresols that ended in death; in both cases, there was significant injury to the gastrointestinal tract.

LD_{50} values in rats were 1,350, 1,800, and 2,020 mg/kg for *o*-, *p*-, and *m*-cresol, respectively, for 10% solutions in olive oil (Deichmann and Witherup 1944). LD_{50} values of 121, 242, and 207 mg/kg were reported for undiluted *o*-, *m*-, and *p*-cresol, respectively, in rats (EI du Pont 1969). Hypoactivity, tremors,

convulsions, salivation, and dyspnea were signs commonly seen preceding death (EI du Pont 1969). Acute LD_{50} values for various cresylic acid formulations in mice ranged from 500 to 2,050 mg/kg (Campbell 1941). Although LD_{50} values were not determined in other species, minimum lethal values were available for a few species; the small number of animals in these studies, however, limits the reliability of these data. In rabbits, minimum lethal values from ingestion ranged from 620 to 1,400 mg/kg for the three isomers (Deichmann and Witherup 1944). In mink, the minimum lethal value of *o*-cresol by gavage was 200 mg/kg, and in ferrets, it was 400 mg/kg (Hornshaw et al. 1986).

Dietary administration of 4,480 mg/kg/day of *o*-cresol to male mice or 5,000 mg/kg/day to female mice for 10 days resulted in the death of 2/5 males and 1/5 females (NTP 1992b). Doses of 4,710 or 4,940 mg/kg/day of *m*-cresol killed 2/5 males and 2/5 female mice, respectively, in a 6-day period (NTP 1992b). A diet containing 30,000 ppm of *p*-cresol (The National Toxicology Program [NTP] did not estimate doses, but were probably 4,000–5,000 mg/kg/day) caused the death of 4/5 male and 5/5 female mice within 1 week in this diet. In the cases of *o*- and *m*-cresol, necropsy of the dead animals did not reveal any notable histopathological changes. In the case of *p*-cresol, lesions were considered secondary to moribund condition or stress, except for liver and kidney necrosis and bone marrow hypocellularity, which could have been related to *p*-cresol (NTP 1992b). Exposure of male F-344 rats or female $B6C3F_1$ mice to up to 720 and 1,040 mg/kg/day, respectively, in the diet for 2 years did not affect survival rates (NTP 2008).

Mortality data were also available for pregnant rats (Tyl 1988a) and rabbits (Tyl 1988b) given cresols by gavage repeatedly during gestation in studies of developmental toxicity. Both *o*- and *p*-cresol produced mortality among rats given 450 mg/kg/day, whereas *m*-cresol did not (Tyl 1988a). In rabbits, *p*-cresol appeared to produce a dose-related increase in mortality at 50–100 mg/kg/day. No deaths occurred in rabbits exposed to *o*- or *m*-cresol (Tyl 1988b).

Exposure to *o*-, *p*-, or *m*-cresol at 450 mg/kg/day by oral gavage produced 12–60% mortality in adult male and female rats in two-generation reproduction studies. The elevated mortality occurred in both the F_0 and F_1 generation adults (Neeper-Bradley and Tyl 1989a, 1989b; Tyl and Neeper-Bradley 1989). In 13-week oral gavage studies of systemic toxicity in rats, elevated mortality resulted only from exposure to *o*-cresol at 600 mg/kg/day (EPA 1988b); in these studies, *p*- and *m*-cresol failed to produce mortality at 450–600 mg/kg/day (EPA 1988c, 1988d).

All reliable LD_{50} and LOAEL values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects of each type in each species and duration category are recorded in Tables 3-1 and plotted in Figure 3-1.

Respiratory Effects. Diffuse necrosis of the bronchial epithelium was noted in a woman who died after drinking 500–750 mL of a concentrated cresol mixture (Labram and Gervais 1968). This effect was thought to have occurred prior to death. Edema and hemorrhage were also observed, but may have occurred secondary to death. Adhesions and fluid were found in the lungs of a woman who died after drinking a disinfectant suspected of containing cresols (Dellal 1931).

Hyperplastic or metaplastic lesions in the respiratory epithelium have been observed in rats orally exposed to cresols for intermediate durations. Epithelial metaplasia of the trachea has been reported to occur in Sprague-Dawley male and female rats treated by gavage with 600 mg/kg/day of *p*-cresol for 13 weeks (EPA 1988c). Fischer-344 rats exposed to doses of up to approximately 2,600 mg/kg/day of *o*-cresol or *m*-cresol in the diet for 28 days had no noticeable histological alterations in tissues of the respiratory tract, including nasal tissues (NTP 1992b). However, exposure of males to ≥835 mg/kg/day or females to ≥770 mg/kg/day of *p*-cresol, or of males to ≥261 mg/kg/day or females to ≥95 mg/kg/day of a mixture of *m*- and *p*-cresol (58/41%) induced dose-related (incidence and severity) hyperplasia of the nasal respiratory epithelium (NTP 1992b). This suggests that *p*-cresol is more potent than the other isomers in inducing this type of lesion. The corresponding NOAELs were 256 and 242 mg/kg/day for *p*-cresol and 90 and 27 mg/kg/day for the mixture. In a 13-week dietary study in rats, similar lesions were seen in males at ≥123 mg/kg/day of the cresol mixture and in females at ≥254 mg/kg/day (NTP 1992b). A NOAEL for males was not identified; the NOAEL for females was 131 mg/kg/day. Neither *m*-cresol nor *p*-cresol alone was tested in the 13-week study. The lesions were observed at the most anterior portions of the nasal septum, dorsal arch, and medial aspect of the nasal turbinates. The hyperplasia was characterized by increased number of goblet cells and pseudogland formation due to the infolding of the hyperplastic cells. The incidence data for nasal lesions in male and female rats exposed for 13 weeks were analyzed via a benchmark dose approach to derive points of departure for deriving an intermediate-duration oral MRL for cresols.

Table 3-1 Levels of Significant Exposure to Cresols - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Wistar)	once (GO)				1350 (LD50, 10% solution in olive oil)	Deichmann and Witherup 1944 ortho	
2	Rat (Wistar)	once (GO)				2020 (LD50, 10% solution in olive oil)	Deichmann and Witherup 1944 meta	
3	Rat (Wistar)	once (GO)				1800 (LD50, 10% solution in olive oil)	Deichmann and Witherup 1944 para	
4	Rat (albino)	once (G)				242 (LD50, undiluted)	EI du Pont 1969 meta	
5	Rat (albino)	once (G)				121 (LD50, undiluted)	EI du Pont 1969 ortho	
6	Rat (albino)	once (G)				207 (LD50, undiluted)	EI du Pont 1969 para	
7	Mouse (NS)	once (GW)				1050 (LD50)	Campbell 1941 mix	
8	Mouse (B6C3F1)	2 wk ad lib (F)				4480 M (2/5 males and 1/5 females died before day 10)	NTP 1992b ortho	

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
9	Mouse (B6C3F1)	2 wk ad lib (F)				4710 M (2/5 males and 2/5 females died before day 6)	NTP 1992b meta	
10	Rabbit (New Zealand)	Gd 6-18 (GO)				100 (5/14 deaths; 0/28 in controls)	Tyl 1988b para	
Systemic								
11	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)	Resp	175 F	450 F (audible respiration)		Tyl 1988a ortho	
			Hepatic	450 F				
			Bd Wt	30 F	175 F (12% decreased body weight gain)	450 F (47% decreased body weight gain during treatment)		
			Other		450 F (15% reduced food intake during treatment)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
12	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)	Resp	175 F	450 F (labored respiration)		Tyl 1988a meta	
			Hepatic	450 F				
			Bd Wt	175 F		450 F (46% decreased body weight gain durng treatment)		
			Other		450 F (13% reduced food intake during treatment)			
13	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)	Resp	175 F	450 F (labored respiration)		Tyl 1988a para	
			Hepatic	450 F				
			Bd Wt	175 F		450 F (40% decreased body weight gain during treatment)		
			Other	175 F		450 F (25% decreased food intake during treatment)		
14	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)	Resp	5 F	50 F (audible respiration)		Tyl 1988b ortho	
			Hepatic	100 F				
			Ocular	5 F	50 F (ocular discharge)			
			Bd Wt	100 F				

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
15	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)	Resp	5	50 (labored respiration)		Tyl 1988b meta	
			Hepatic	100				
			Ocular	5	50 (ocular discharge			
			Bd Wt	100				
16	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)	Resp	5 F	50 F (labored breathing)		Tyl 1988b para	
			Hepatic	100 F				
			Ocular	5 F	50 F (ocular discharge)			
			Bd Wt	100 F				
Neurological								
17	Rat (CD)	2 wk 7 d/wk (GO)			50 (CNS stimulation)	600 (convulsions)	TRL 1986 ortho	
18	Rat (CD)	2 wk 7 d/wk (GO)			50 (CNS stimulation)	600 (convulsions)	TRL 1986 para	
19	Rat (CD)	2 wk 7 d/wk (GO)			50 (CNS stimulation)	450 (convulsions)	TRL 1986 meta	
20	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		175		450 (ataxia, tremors, hypoactivity)	Tyl 1988a ortho	

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
21	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		175		450 (ataxia, tremors hypoactivity)	Tyl 1988a meta	
22	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		175		450 (ataxia, tremors hypoactivity)	Tyl 1988a para	
23	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		5	50 (hypoactivity)		Tyl 1988b ortho	
24	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		5	50 (hypoactivity)		Tyl 1988b para	
25	Mink (NS)	once (G)		50		100 (incoordination)	Hornshaw et al. 1986 ortho	
26	Ferret (NS)	once (G)				200 (incoordination)	Hornshaw et al. 1986 ortho	
Reproductive								
27	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		450			Tyl 1988a ortho	NOAEL is for uterine weight and number of corpora lutea.
28	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		450			Tyl 1988a meta	NOAEL is for uterine weight and number of corpora lutea.

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
29	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		450			Tyl 1988a para	NOAEL is for uterine weight and corpora lutea.
30	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		100			Tyl 1988b ortho	NOAEL is for uterine weight and number of corpora lutea.
31	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		100			Tyl 1988b meta	NOAEL is for uterine weight and number of corpora lutea.
32	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		100			Tyl 1988b para	NOAEL is for uterine weight and number of corpora lutea.
Developmental								
33	Rat (Sprague-Dawley)	Gd 11 once (G)		1000			Kavlock 1990 para	NOAEL is for postimplantation loss, litter size, viability, and postnatal weight.
34	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		175	450 (increased incidence of skeletal variations)		Tyl 1988a ortho	

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
35	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		450			Tyl 1988a meta	NOAEL is for embryotoxicity and teratogenicity.
36	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		175	450 (increased incidence of skeletal variations)		Tyl 1988a para	
37	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		50	100 (delayed ossification)		Tyl 1988b ortho	
38	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		100			Tyl 1988b meta	NOAEL is for embryotoxicity and teratogenicity.
39	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		100			Tyl 1988b para	NOAEL is for embryotoxicity and teratogenicity.
INTERMEDIATE EXPOSURE								
Death								
40	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (GO)				600 (death of 19 females and 9 males out of 30 rats/sex)	EPA 1988b ortho	
41	Rat (CD)	10 wk 5 d/wk (GO)				450 (death of 8/25 males and 5/25 females)	Neeper-Bradley and Tyl 1989a para	

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
42	Rat (CD)	10 wk 5 d/wk (GO)				450	(death of 7 males and 5 females out of 25/sex)	Neeper-Bradley and Tyl 1989b meta	
43	Rat (CD)	10-11 wk 5 d/wk (GO)				450	(32-60% mortality in F0 and F1 adults)	Tyl and Neeper-Bradley 1989 ortho	
Systemic									
44	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (GO)	Resp	600				EPA 1988b ortho	NOAELs are for organ weights and histopathology.
			Cardio	600					
			Gastro	600					
			Hemato	600					
			Musc/skel	600					
			Hepatic	600					
			Renal	600					
			Endocr	600					
			Ocular	600					
			Bd Wt	175 M	600 M	(11% decreased body weight gain)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
45	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (GO)	Resp	175	600	(epithelial metaplasia in trachea)			EPA 1988c para	
			Cardio	600						
			Gastro	600						
			Hemato	50 F	175 F	(6-8% decreased red blood cell count and hemoglobin)				
			Musc/skel	600						
			Hepatic	175	600	(increased SGOT, SGPT; inflammation)				
			Renal		50	(nephropathy)				
			Endocr	600						
			Ocular	600						
			Bd Wt	175 M			600 M	(21% decreased body weight gain)		

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
46	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (GO)	Resp	450			EPA 1988d meta	NOAELs are for organ weights and histopathology.
			Cardio	450				
			Gastro	450				
			Hemato	450				
			Musc/skel	450				
			Hepatic	450				
			Renal	450				
			Endocr	450				
			Ocular	450				
			Bd Wt	50 M		150 M (22% decreased body weight gain)		
47	Rat (Sprague-Dawley)	28 d 1 x/d (GO)	Hemato	1000			Koizumi et al. 2003 meta	NOAELs are for histopathology of liver and kidney and a number of hematology end points.
			Hepatic	1000				
			Renal	1000				
			Bd Wt	300	1000 F (11% reduced final body weight)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
48	Rat (CD)	10-11 wk 5 d/wk (GO)	Bd Wt	175 M	450 M (13% reduced final body weight)		Neeper-Bradley and Tyl 1989a para	
49	Rat (CD)	10 wk 5 d/wk (GO)	Bd Wt	175 M	450 M (15% decreased final body weight)		Neeper-Bradley and Tyl 1989b meta	
50	Rat (Fischer- 344)	28 d ad lib (F)	Resp	2610 M			NTP 1992b ortho	NOAELs are for organ weights and histopathology.
			Cardio	2610 M				
			Gastro	2610 M				
			Musc/skel	2610 M				
			Hepatic	266 M	861 M (25% increase absolute liver weight and 23% in relative)			
			Renal	266 M	861 M (15% increase in absolute kidney weight and 13% in relative)			
			Endocr	2610 M				
			Dermal	2610 M				
			Bd Wt	881 F	2510 F (12% reduction in final body weight)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
51	Rat (Fischer- 344)	28 d ad lib (F)	Resp	2470 M			NTP 1992b meta	NOAELs are for organ weights and histopathology.
			Cardio	2470 M				
			Gastro	2470 M				
			Musc/skel	2470 M				
			Hepatic	252 M	870 M (16% increase in absolute and relative liver weight)			
			Renal	2470 M				
			Endocr	2470 M				
			Dermal	2470 M				
			Bd Wt	862 F	2310 F (16% reduced final body weight)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
52	Rat (Fischer- 344)	28 d ad lib (F)	Resp	242 F	770 F (respiratory nasal epithelium hyperplasia)		NTP 1992b para	NOAELs are for organ weights and histopathology.
			Cardio	2180 M				
			Gastro	2180 M				
			Hemato	770 F	2060 F (bone marrow hypocellularity)			
			Musc/skel	2180 M				
			Hepatic	83 F	242 F (16% increase absolute liver weight)			
			Renal	2180 M				
			Endocr	2180 M				
			Dermal	2180 M				
			Bd Wt	835 M	2060 F (16% reduced final body weight)	2180 M (30% reduced final body weight)		

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
53	Rat (Fischer- 344)	28 d ad lib (F)	Resp	27 F	95 F (hyperplasia in respiratory nasal epithelium)		NTP 1992b mix	NOAELs are for organ weights and histopathology.
			Cardio	2600 M				
			Gastro	90 M	261 F (hyperplasia and hyperkeratosis of esophageal epithelium)			
			Hemato	886 M	2570 M (bone marrow hypocellularity)			
			Musc/skel	2600 M				
			Hepatic	261 M	877 M (16-20% increase in absolute and relative liver weight)			
			Renal	2600 M				
			Endocr	90 M	261 M (increased colloid in thyroid follicular cell)			
			Dermal	2600 M				
			Bd Wt	877 M	2600 M (18% reduced final body weight)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
54	Rat (Fischer- 344)	13 wk ad lib (F)	Resp	2028 M			NTP 1992b ortho	NOAELs are for organ weights and histopathology.
			Cardio	2028 M				
			Gastro	2028 M				
			Hemato	513 F	1021 F (bone marrow hypocellularity)			
			Musc/skel	2028 M				
			Hepatic	247 M	510 M (10-12% increase in absolute and relative liver weight)			
			Renal	2028 M				
			Endocr	2028 M				
			Dermal	2028 M				
			Bd Wt	1021 F	2024 F (15% reduced final body weight)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
55	Rat (Fischer- 344)	13 wk ad lib (F)	Resp		123[b] M (3/10 with minimal hyperplasia in the nasal respiratory epithelium vs. 0/10 in controls)		NTP 1992b mix	NOAELs are for organ weights and histopathology.
			Cardio	2050 F				
			Gastro	2050 F				
			Hemato	991 M	2014 M (bone marrow hypocellularity)			
			Musc/skel	2050 F				
			Hepatic	241 M	486 M (11-12% increase in absolute and relative liver weight)			
			Renal	2050 F				
			Endocr	254 F	509 F (increased colloid in thyroid follicular cells)			
			Dermal	2050 F				
			Bd Wt	991 M	2014 M (17% reduced final body weight)			
56	Rat (CD)	10 wk 5 d/wk (GO)	Bd Wt	175 M	450 M (10% decreased final body weight)		Tyl and Neeper-Bradley 1989 ortho	

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
57	Mouse (B6C3F1)	28 d ad lib (F)	Resp	1650 M	4480 M (rapid breathing)		NTP 1992b ortho	NOAELs are for organ weights and histopathology.
			Cardio	5000 F				
			Gastro	5000 F				
			Musc/skel	5000 F				
			Hepatic	5000 F				
			Renal	5000 F				
			Endocr	5000 F				
			Dermal	5000 F				
			Bd Wt	1650 M		4480 M (28% reduction in final weight)		

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
58	Mouse (B6C3F1)	28 d ad lib (F)	Resp	651 F	2080 F (labored respiration)		NTP 1992b meta	NOAELs are for organ weights and histopathology.
			Cardio	4940 F				
			Gastro	4940 F				
			Musc/skel	4940 F				
			Hepatic	4940 F				
			Renal	4940 F				
			Endocr	4940 F				
			Dermal	4940 F				
			Bd Wt	1730 M		4710 M (21% reduction in final weight)		

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
59	Mouse (B6C3F1)	28 d ad lib (F)	Resp	50 M	163 M (3/5 with minimal hyperplasia of nasal respiratory epithelium vs. 0/5 in controls)		NTP 1992b para	NOAELs are for organ weights and histopathology.
			Cardio	1590 F				
			Gastro	1590 F				
			Hemato	1590 F				
			Musc/skel	1590 F				
			Hepatic	564 F	1590 F (15-20% increase in relative and absolute liver weight)			
			Renal	1590 F				
			Endocr	1590 F				
			Dermal	1590 F				
			Bd Wt	469 M	1410 M (17% reduced final body weight)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
60	Mouse (B6C3F1)	28 d ad lib (F)	Resp	200 F	604 F (3/5 with minimal hyperplasia of the nasal respiratory epithelium vs. 0/5 in controls)		NTP 1992b mix	NOAELs are for organ weights and histopathology.
			Cardio	4730 F				
			Gastro	4730 F				
			Hemato	1490 M	4530 M (bone marrow hypocellularity)			
			Musc/skel	4730 F				
			Hepatic	604 F	1880 F (30% increase in absolute and relative liver weight)			
			Renal	4730 F				
			Endocr	4730 F				
			Dermal	1490 M	4530 M (alopecia)			
			Bd Wt	471 M	1490 M (10% reduced final body weight)	4530 M (27% reduction in final weight)		

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
61	Mouse (B6C3F1)	13 wk ad lib (F)	Resp	3205 F			NTP 1992b ortho	NOAELs are for organ weights and histopathology.
			Cardio	3205 F				
			Gastro	1723 M	2723 M (forestomach epithelial hyperplasia)			
			Hemato	3205 F				
			Musc/skel	3205 F				
			Hepatic	794 M	1723 M (17-19% increase in absolute and relative liver weight)			
			Renal	3205 F				
			Endocr	3205 F				
			Dermal	3205 F				
			Bd Wt	1723 M	2723 M (16% reduced final body weight)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
62	Mouse (B6C3F1)	13 wk ad lib (F)	Resp	402 M	776 M (4/10 with minimal hyperplasia of the nasal respiratory epithelium vs. 1/10 in controls)		NTP 1992b mix	NOAELs are for organ weights and histopathology.
			Cardio	1693 F				
			Gastro	1693 F				
			Hemato	1693 F				
			Musc/skel	1693 F				
			Hepatic	402 M	776 M (12% increase in absolute and relative liver weight)			
			Renal	1693 F				
			Endocr	1693 F				
			Dermal	1693 F				
			Bd Wt	1693 F				
63	Hamster (Golden Syrian)	20 wk ad lib (F)	Gastro		1415 M (mild to moderate forestomach hyperplasia)		Hirose et al. 1986 para	
			Hepatic	1415 M				

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
64	Ferret (NS)	28 d (F)	Resp	400			Hornshaw et al. 1986 ortho	NOAELs are for organ weights and gross necropsy.
			Cardio	400				
			Hemato	400				
			Hepatic	400				
			Renal	400				
			Bd Wt	400				
65	Mink (NS)	28 d (F)	Resp	320			Hornshaw et al. 1986 ortho	NOAELs are for organ weights and gross necropsy.
			Cardio	320				
			Hemato	320				
			Hepatic	320				
			Renal	320				
			Bd Wt			320 F (weight loss)		
Immuno/ Lymphoret								
66	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (GO)		600			EPA 1988b ortho	NOAEL is for weight and histopathology of spleen, thymus and lymph nodes.

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
67	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (GO)		600			EPA 1988c para	NOAEL is for changes in histopathology of spleen, thymus, and lymph nodes.
68	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (GO)		450			EPA 1988d meta	NOAEL is for changes in weight and histopathology of spleen, thymus, and lymph nodes.
69	Rat (Fischer- 344)	28 d ad lib (F)		2610 M			NTP 1992b ortho	NOAEL is for weight and histopathology of lymphoreticular organs.
70	Rat (Fischer- 344)	28 d ad lib (F)		2470 M			NTP 1992b meta	NOAEL is for lymphoreticular organs weights and histopathology.
71	Rat (Fischer- 344)	28 d ad lib (F)		2180 M			NTP 1992b para	NOAEL is for lymphoreticular organs weights and histopathology.
72	Rat (Fischer- 344)	13 wk ad lib (F)		2028 M			NTP 1992b ortho	NOAELs are for weight and histopathology of lymphoreticular organs.

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
73	Rat (Fischer- 344)	13 wk ad lib (F)		2050 F			NTP 1992b mix	NOAEL is for weight and histopathology of lymphoreticular organs.
74	Rat (Fischer- 344)	28 d ad lib (F)		2600 M			NTP 1992b mix	NOAEL is for weight and histopathology of lymphoreticular organs.
75	Mouse (B6C3F1)	28 d ad lib (F)		5000 F			NTP 1992b ortho	NOAELs are for weight and histopathology of lymphoreticular organs.
76	Mouse (B6C3F1)	28 d ad lib (F)		4940 F			NTP 1992b meta	NOAELs are for weight and histopathology of lymphoreticular organs.
77	Mouse (B6C3F1)	28 d ad lib (F)		1590 F			NTP 1992b para	NOAEL is for weight and histopathology of lymphoreticular organs.
78	Mouse (B6C3F1)	28 d ad lib (F)		4730 F			NTP 1992b mix	NOAEL is for weights and histopathology of lymphoreticular organs.

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
79	Mouse (B6C3F1)	13 wk ad lib (F)		3205 F			NTP 1992b ortho	NOAEL is for weight and histopathology of lymphoreticular organs.
80	Mouse (B6C3F1)	13 wk ad lib (F)		1693 F			NTP 1992b mix	NOAEL is for weight and histopathology of lymphoreticular organs.
Neurological								
81	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (GO)		175		600 (coma, convulsions)	EPA 1988b ortho	
82	Rat	13 wk 7 d/wk 1 x/d (GO)		175		600 (convulsions, coma)	EPA 1988c para	
83	Rat	13 wk 7 d/wk 1 x/d (GO)		150		450 (lethargy, tremors)	EPA 1988d meta	
84	Rat (Sprague-Dawley)	28 d 1 x/d (GO)		300		1000 (salivation and tremors)	Koizumi et al. 2003 meta	
85	Rat (CD)	10 wk 5 d/wk (GO)		30	175 (perioral wetness)		Neeper-Bradley and Tyl 1989a para	

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
86	Rat (CD)	10 wk 5 d/wk (GO)		30	175 (perioral wetness)		Neeper-Bradley and Tyl 1989b meta	
87	Rat (Fischer- 344)	28 d ad lib (F)		2610 M			NTP 1992b ortho	NOAEL is for histopathology of the brain and clinical signs.
88	Rat (Fischer- 344)	28 d ad lib (F)		2470 M			NTP 1992b meta	NOAEL is for weight and histopathology of the brain and clinical signs.
89	Rat (Fischer- 344)	28 d ad lib (F)		2180 M			NTP 1992b para	NOAEL is for weight and histopathology of the brain and clinical signs.
90	Rat (Fischer- 344)	13 wk ad lib (F)		2028 M			NTP 1992b ortho	NOAEL is for weight and histopathology of the brain and clinical signs.
91	Rat (Fischer- 344)	13 wk ad lib (F)		2050 F			NTP 1992b mix	NOAEL is for weight and histopathology of the brain and clinical signs.

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
92	Rat (Fischer- 344)	28 d ad lib (F)		2600 M			NTP 1992b mix	NOAEL is for histopathology of the brain and clinical signs.
93	Rat (CD)	13 wk 7 d/wk (GO)			50 (CNS stimulation)	450 (convulsions)	TRL 1986 ortho	Behavioral tests done throughout the study had sporadic non dose-related differences with controls.
94	Rat (CD)	13 wk 7 d/wk (GO)			50 (CNS stimulation)	600 (convulsions)	TRL 1986 para	Behavioral tests done throughout the study had sporadic non dose-related differences with controls.
95	Rat (CD)	13 wk 7 d/wk (GO)			50 (hypoactivity)	450 (convulsions)	TRL 1986 meta	Behavioral tests done throughout the study had sporadic non dose-related differences with controls.
96	Rat (CD)	10-11 wk 5 d/wk 6-9 wk 7 d/wk (GO)		30		175 (ataxia, hypoactivity)	Tyl and Neeper-Bradley 1989 ortho	

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
97	Mouse (B6C3F1)	28 d ad lib (F)		1650 M	4480 M (lethargy and tremors)		NTP 1992b ortho	
98	Mouse (B6C3F1)	28 d ad lib (F)		651 F	2080 F (lethargy)		NTP 1992b meta	
99	Mouse (B6C3F1)	28 d ad lib (F)		469 M	1410[c] M (lethargy) 1590 F		NTP 1992b para	
100	Mouse (B6C3F1)	28 d ad lib (F)		1490 M	4530 M (lethargy)		NTP 1992b mix	
101	Mouse (B6C3F1)	13 wk ad lib (F)		3205 F			NTP 1992b ortho	NOAEL is for weight and histopathology of the brain.
102	Mouse (B6C3F1)	13 wk ad lib (F)		1693 F			NTP 1992b mix	NOAEL is for weight and histopathology of the brain.

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
103	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (GO)		600			EPA 1988b ortho	NOAEL is for weight and histopathology of reproductive organs. Fertility was not assessed.
104	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (GO)		600			EPA 1988c para	NOAEL is for histopathology of reproductive organs. Fertility was not assessed.
105	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (GO)		450			EPA 1988d meta	NOAEL is for changes in weight and histopathology of reproductive organs.
106	Rat (CD)	10 wk 5 d/wk (GO)		450			Neeper-Bradley and Tyl 1989a para	The NOAEL is for reproductive function end points in both sexes.
107	Rat (CD)	10 wk 5 d/wk (GO)		450			Neeper-Bradley and Tyl 1989b meta	The NOAEL is for reproductive function end points in both sexes.

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
108	Rat (Fischer- 344)	28 d ad lib (F)		2610 M			NTP 1992b ortho	NOAEL is for weight and histopathology of reproductive organs; fertility was not assessed.
109	Rat (Fischer- 344)	28 d ad lib (F)		2470 M 862 F[c]	2310 F (mild uterine atrophy in 4/5 females)		NTP 1992b meta	Fertility was not assessed.
110	Rat (Fischer- 344)	28 d ad lib (F)		2180 M 770 F[c]	2060 F (mild to moderate uterine atrophy)		NTP 1992b para	Fertility was not assessed.
111	Rat (Fischer- 344)	13 wk ad lib (F)		2028 M			NTP 1992b ortho	NOAEL is for weight and histopathology of reproductive organs, sperm effects, and estrous cycle length.
112	Rat (Fischer- 344)	13 wk ad lib (F)		2014 M 254 F[c]	509 F (lengthened estrous cycle)		NTP 1992b mix	
113	Rat (Fischer- 344)	28 d ad lib (F)		2600 M			NTP 1992b mix	NOAEL is for histopathology of reproductive organs.

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
114	Rat (CD)	10 wk 5 d/wk (GO)		450			Tyl and Neeper-Bradley 1989 ortho	The NOAEL is for reproductive function end points in both sexes.
115	Mouse (CD-1)	14 wk ad lib (F)		660			NTP 1992a ortho	NOAEL is for reproductive functional end points in a study using a continuous breeding protocol.
116	Mouse (B6C3F1)	28 d ad lib (F)		4480 M 763[c] F	1670 F (mild atrophy of the uterus in 5/5 mice)		NTP 1992b ortho	Fertility was not assessed.
117	Mouse (B6C3F1)	28 d ad lib (F)		4710 M 2080[c] F		4940 F (mild to moderate atrophy of mammary gland, uterus, and ovaries)	NTP 1992b meta	Fertility was not assessed.
118	Mouse (B6C3F1)	28 d ad lib (F)		1590 F			NTP 1992b para	NOAEL is for weight and histopathology of reproductive organs; fertility was not assessed.

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
119	Mouse (B6C3F1)	28 d ad lib (F)		4730 F			NTP 1992b mix	NOAEL is for weight and histopathology of reproductive organs; fertility was not assessed.
120	Mouse (B6C3F1)	13 wk ad lib (F)		2723 M 1663[c] F	3205 F (lengthened estrous cycle)		NTP 1992b ortho	Fertility was not assessed.
121	Mouse (B6C3F1)	13 wk ad lib (F)		1693 F			NTP 1992b mix	NOAEL is for weight and histopathology of reproductive organs, sperm effects, and estrous cycle length.
122	Mouse (CD-1)	14 wk ad lib (F)		1390	1682 (increased cumulative days to litter)		NTP 1992c mix	No histopathology in reproductive organs from males or females. Fertility of F1 not altered.
123	Mink (NS)	6 mo (F)		105			Hornshaw et al. 1986 ortho	NOAEL is for reproductive function end points in males and females.

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
Developmental									
124	Rat (Sprague-Dawley)	18 d 1 x/d pnd 4-21 (GO)		30		100	(tremors under contact stimulus)	Koizumi et al. 2003 meta	Tremors observed in newborn rats but not in 5-week old exposed for 28 days.
125	Rat (CD)	10 wk 5 d/wk (GO)		175		450	(reduced viability of F1 generation)	Neeper-Bradley and Tyl 1989a para	
126	Rat (CD)	10 wk 5 d/wk (GO)		175		450	(reduced viability of F1 generation)	Neeper-Bradley and Tyl 1989b meta	
127	Rat (CD)	10 wk 5 d/wk (GO)		175		450	(reduced viability of F1 generation)	Tyl and Neeper-Bradley 1989 ortho	
128	Mouse (CD-1)	14 wk ad lib (F)		1390		1682	(decreased number of live pups/litter)	NTP 1992c mix	

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
129	Rat (Fischer- 344)	2 yr ad lib (F)	Resp		123 M (17/50 with minimal hyperplasia of the nasal respiratory epithelium, 3/50 in controls)		NTP 2008 mixed	The LOAEL for respiratory is listed as 123 mg/kg/day, which was the mean dose during the first 13 weeks when the nose lesions probably developed.
			Cardio	720 M				
			Gastro	720 M				
			Musc/skel	720 M				
			Hepatic	230 M	720 M (increased incidence of eosinophilic foci)			
			Renal	230 M	720 M (transitional epithelial hyperplasia of the renal pelvis)			
			Endocr	720 M				
			Dermal	720 M				
			Ocular	720 M				
			Bd Wt	230 M	720 M (final body weight reduced 15%)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
130	Mouse (B6C3F1)	2 yr ad lib (F)	Resp		100[d] F (42/50 with minimal bronchiolar hyperplasia, 0/50 in controls)		NTP 2008 mixed	NOAELs are for histopathology of tissues and organs.
			Cardio	1040 F				
			Gastro	1040 F				
			Musc/skel	1040 F				
			Hepatic	300 F	1040 F (increased eosinophilic foci)			
			Renal	1040 F				
			Endocr		100 F (follicular degeneration in thyroid gland)			
			Dermal	1040 F				
			Ocular	1040 F				
			Bd Wt	100 F	300 F (11% reducton in final body weight)	1040 F (24% reduction in final body weight)		
Immuno/ Lymphoret								
131	Rat (Fischer- 344)	2 yr ad lib (F)		720 M			NTP 2008 mixed	NOAEL is for histopathological alterations of lymphoreticular organs.

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
132	Mouse (B6C3F1)	2 yr ad lib (F)		1040 F			NTP 2008 mixed	NOAEL is for histopathology of lymphoreticular organs.
Neurological								
133	Rat (Fischer- 344)	2 yr ad lib (F)		720 M			NTP 2008 mixed	NOAEL is for histopathology of the brain.
134	Mouse (B6C3F1)	2 yr ad lib (F)		1040 F			NTP 2008 mixed	NOAEL is for histopathology of the brain.
Reproductive								
135	Rat (Fischer- 344)	2 yr ad lib (F)		720 M			NTP 2008 mixed	NOAEL is for histopathology of the reproductive organs.
136	Mouse (B6C3F1)	2 yr ad lib (F)		1040 F			NTP 2008 mixed	NOAEL is for histopathology of reproductive organs.

Table 3-1 Levels of Significant Exposure to Cresols - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Cancer								
137	Mouse (B6C3F1)	2 yr ad lib (F)				1040 F (CEL: squamous cell papilloma in forestomach, 0/50, 1/50, 1/49, 10/50)	NTP 2008 mixed	

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

b Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.1 mg/kg/day; the MRL was derived by dividing the BMDL10 of 13.94 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 to protect sensitive subpopulations).

c Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

d Used to derive a chronic-duration oral minimal risk level (MRL) of 0.1 mg/kg/day; the MRL was derived by dividing the LOAEL of 100 mg/kg/day by an uncertainty factor of 1000 (10 for animal to human extrapolation, 10 for use of a LOAEL, and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; BMDL = below minimum detectable limits; Cardio = cardiovascular; CNS = central nervous system; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; gd = gestational day; (GO) = gavage in oil; (GW) = gavage in water; hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculo/skeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; pnd = post-natal day; Resp = respiratory; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; x = time(s); wk = week(s)

Figure 3-1 Levels of Significant Exposure to Cresols - Oral

Acute (≤14 days)

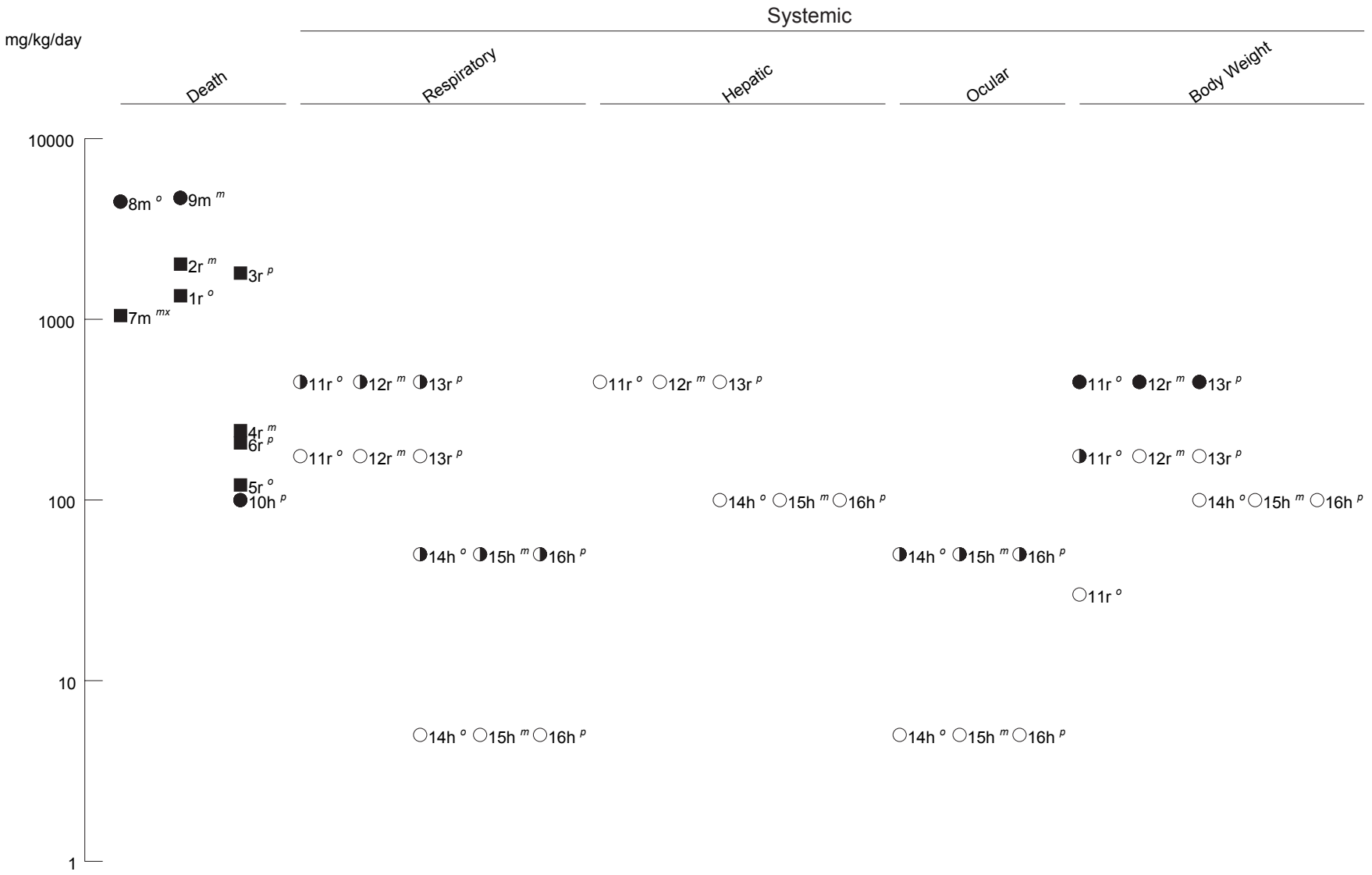


Figure 3-1 Levels of Significant Exposure to Cresols - Oral *(Continued)*

Acute (≤14 days)

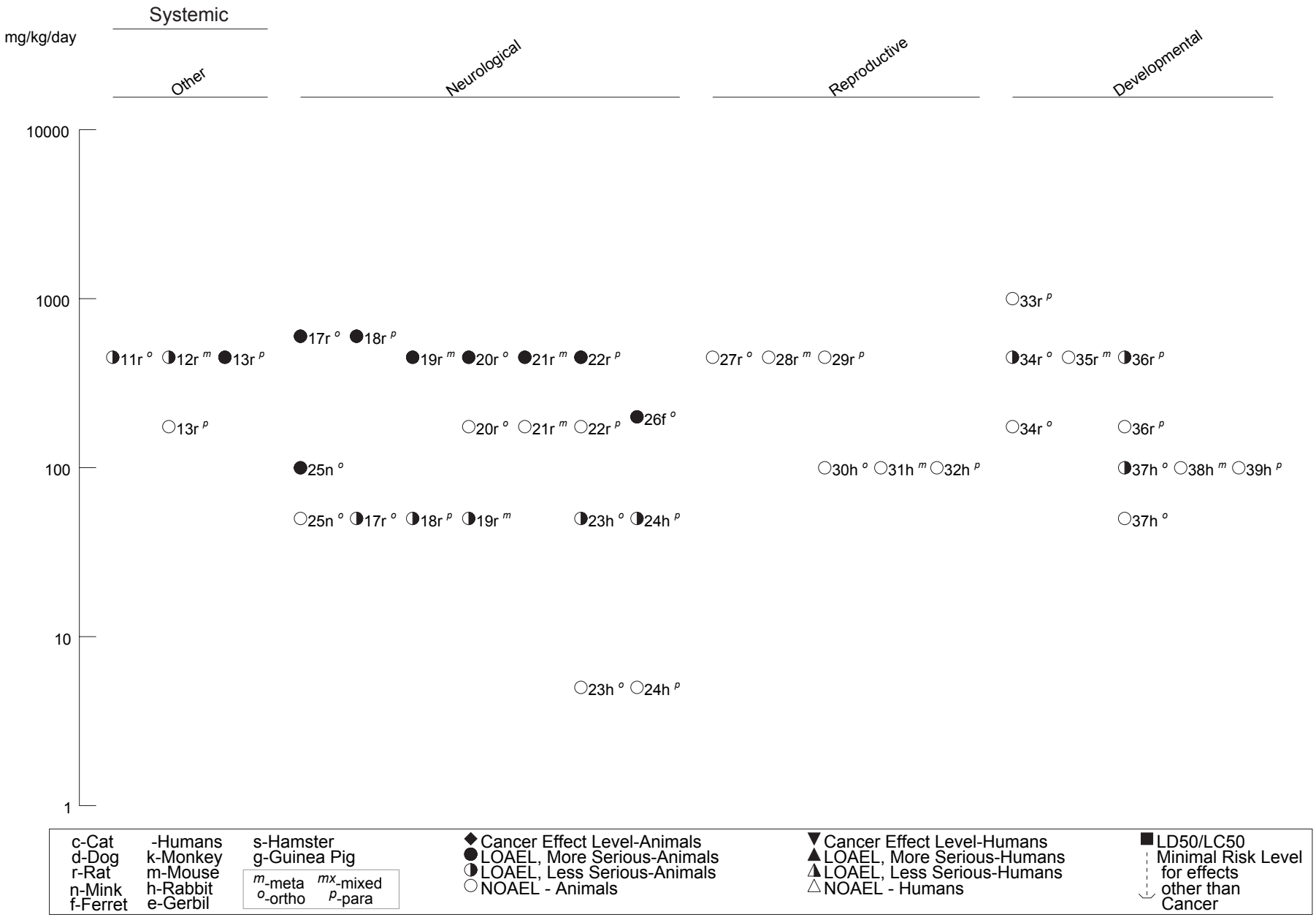


Figure 3-1 Levels of Significant Exposure to Cresols - Oral *(Continued)*

Intermediate (15-364 days)

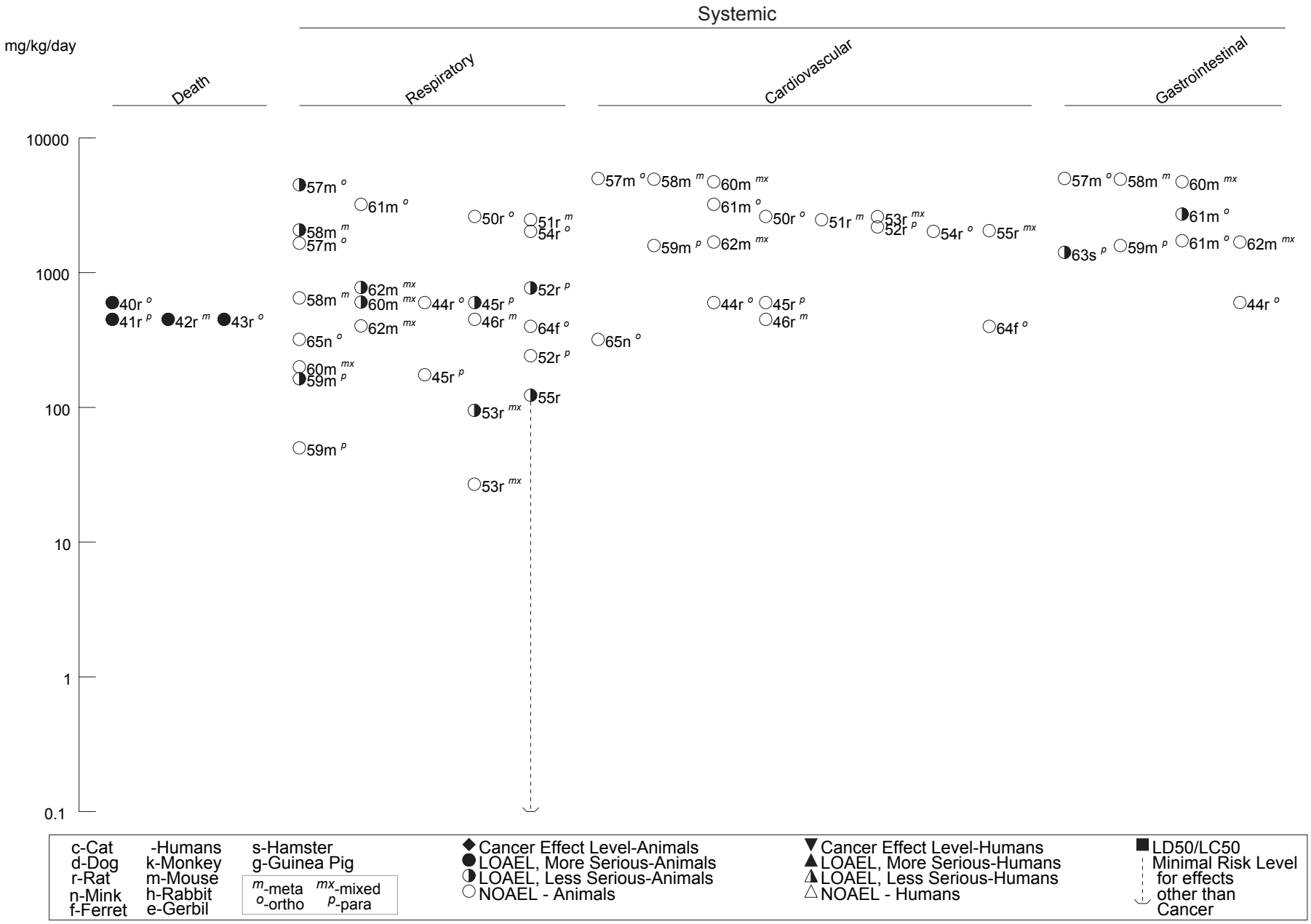


Figure 3-1 Levels of Significant Exposure to Cresols - Oral *(Continued)*

Intermediate (15-364 days)

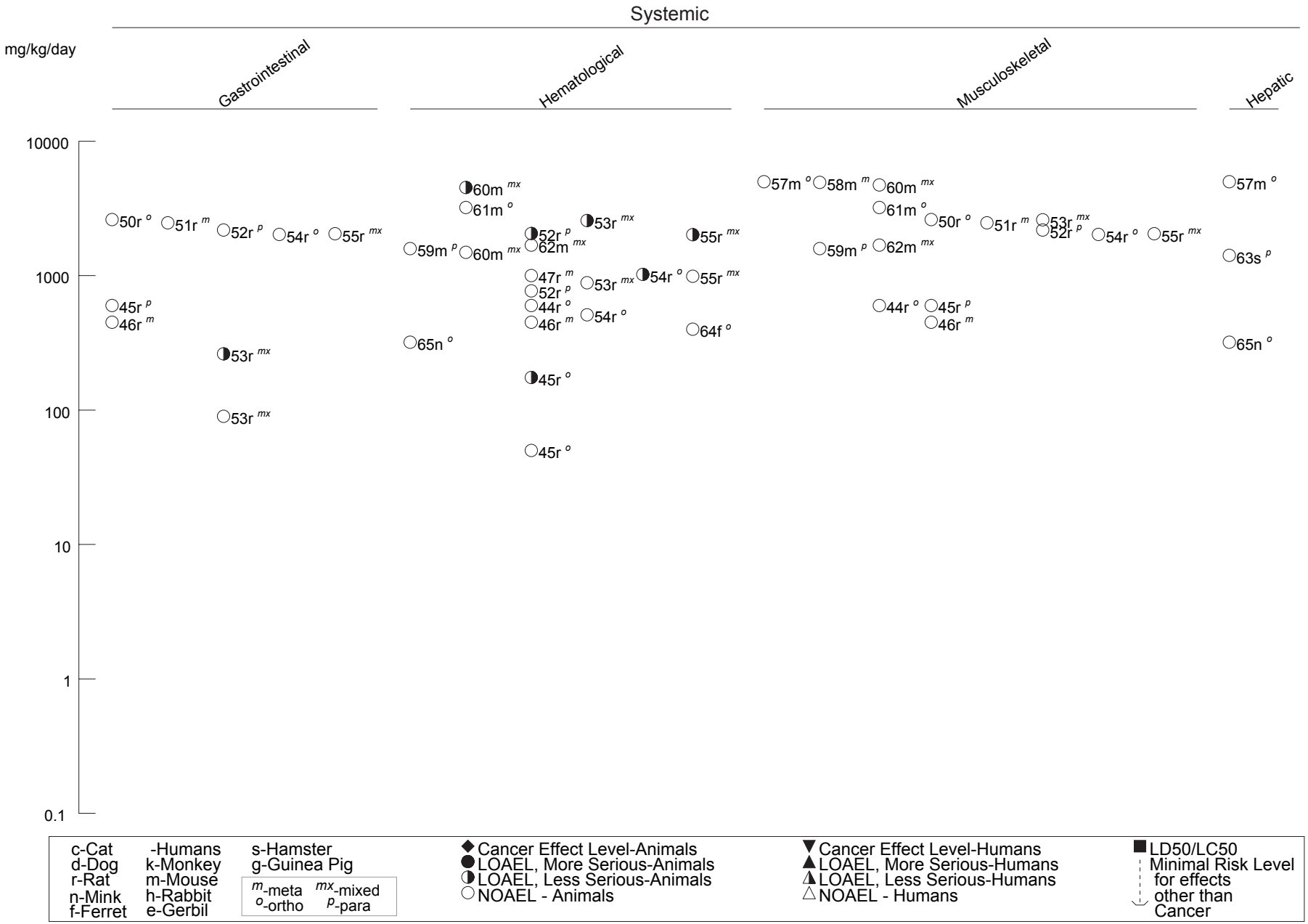


Figure 3-1 Levels of Significant Exposure to Cresols - Oral *(Continued)*

Intermediate (15-364 days)

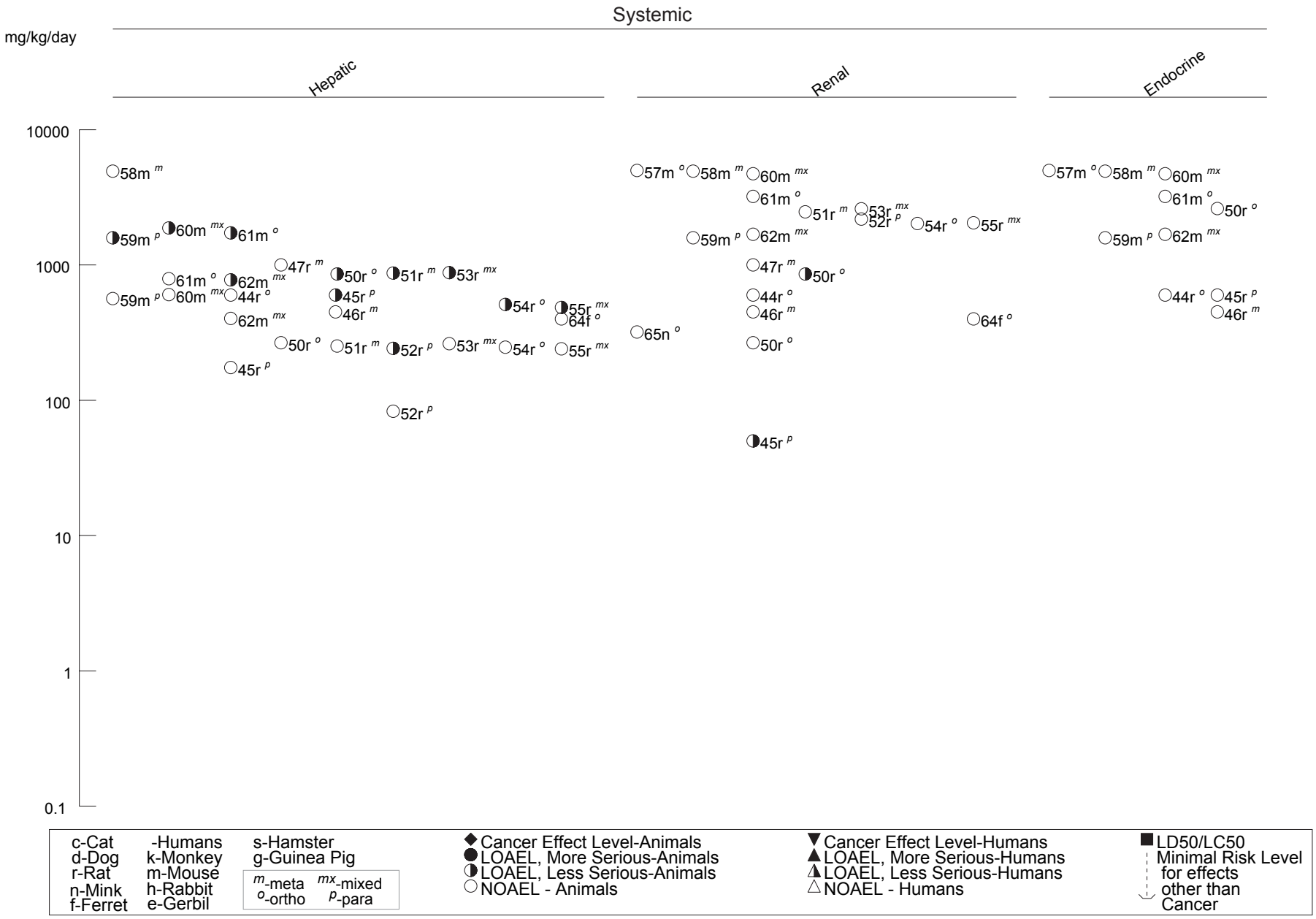


Figure 3-1 Levels of Significant Exposure to Cresols - Oral *(Continued)*

Intermediate (15-364 days)

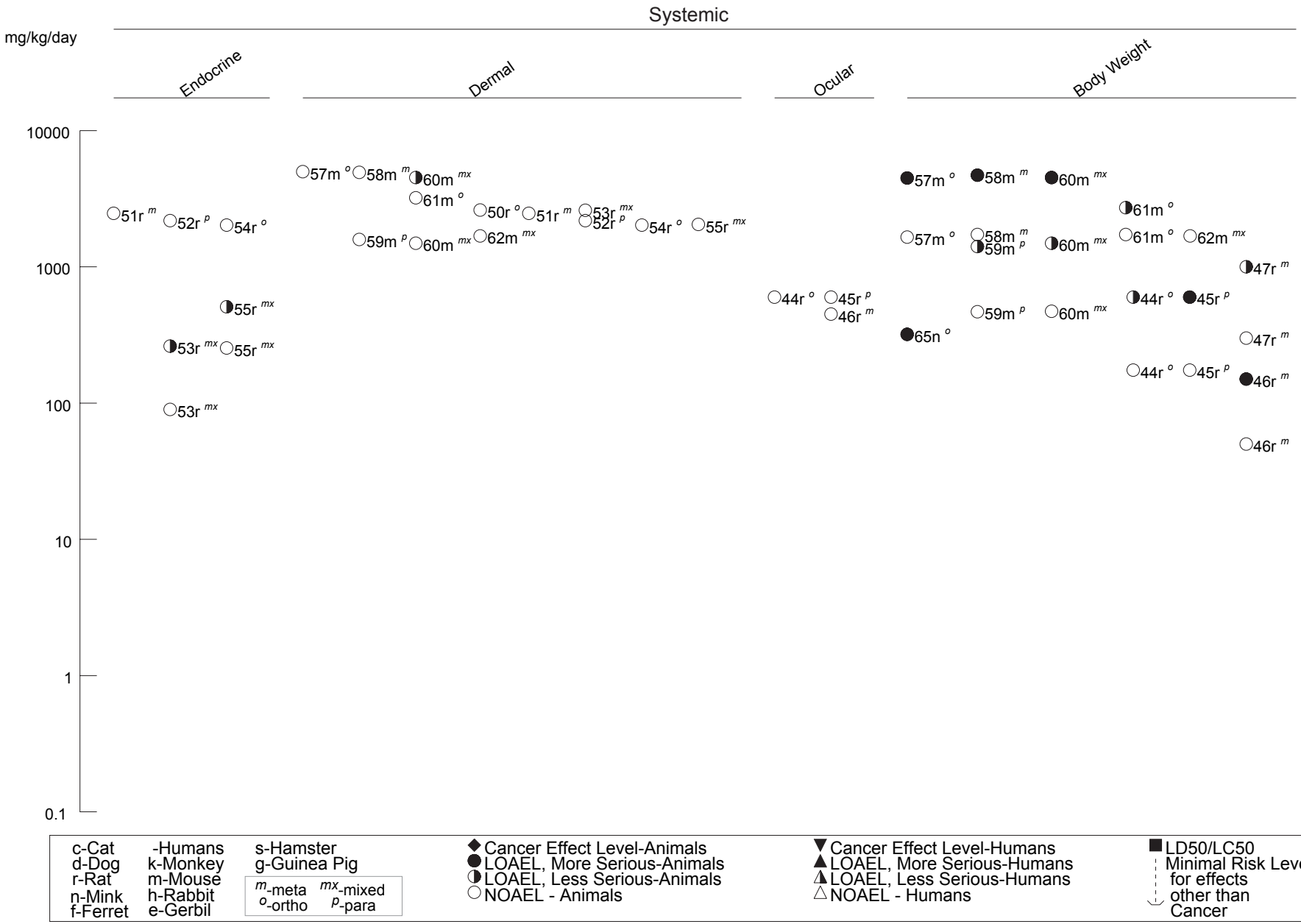


Figure 3-1 Levels of Significant Exposure to Cresols - Oral *(Continued)*

Intermediate (15-364 days)

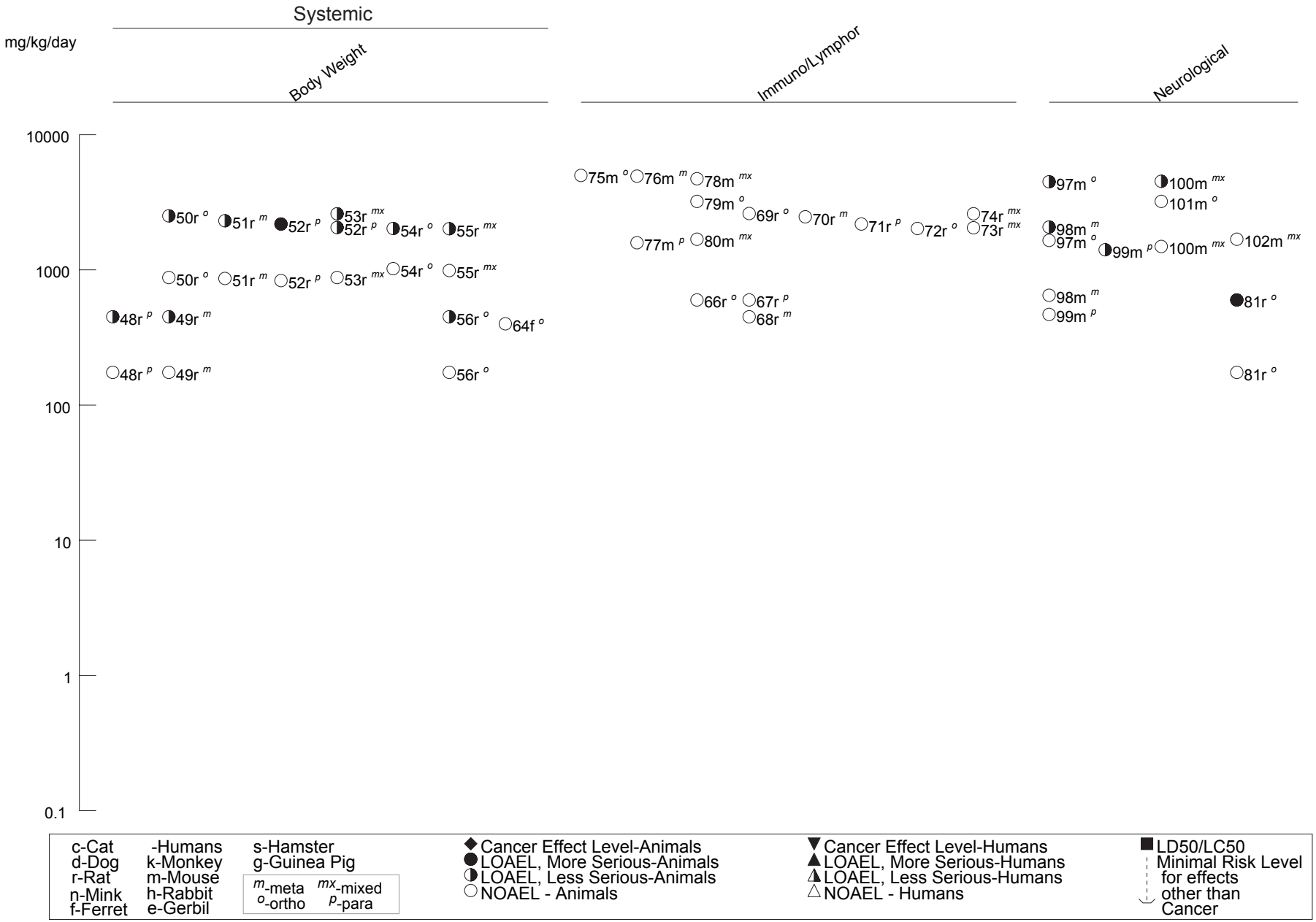


Figure 3-1 Levels of Significant Exposure to Cresols - Oral *(Continued)*

Intermediate (15-364 days)

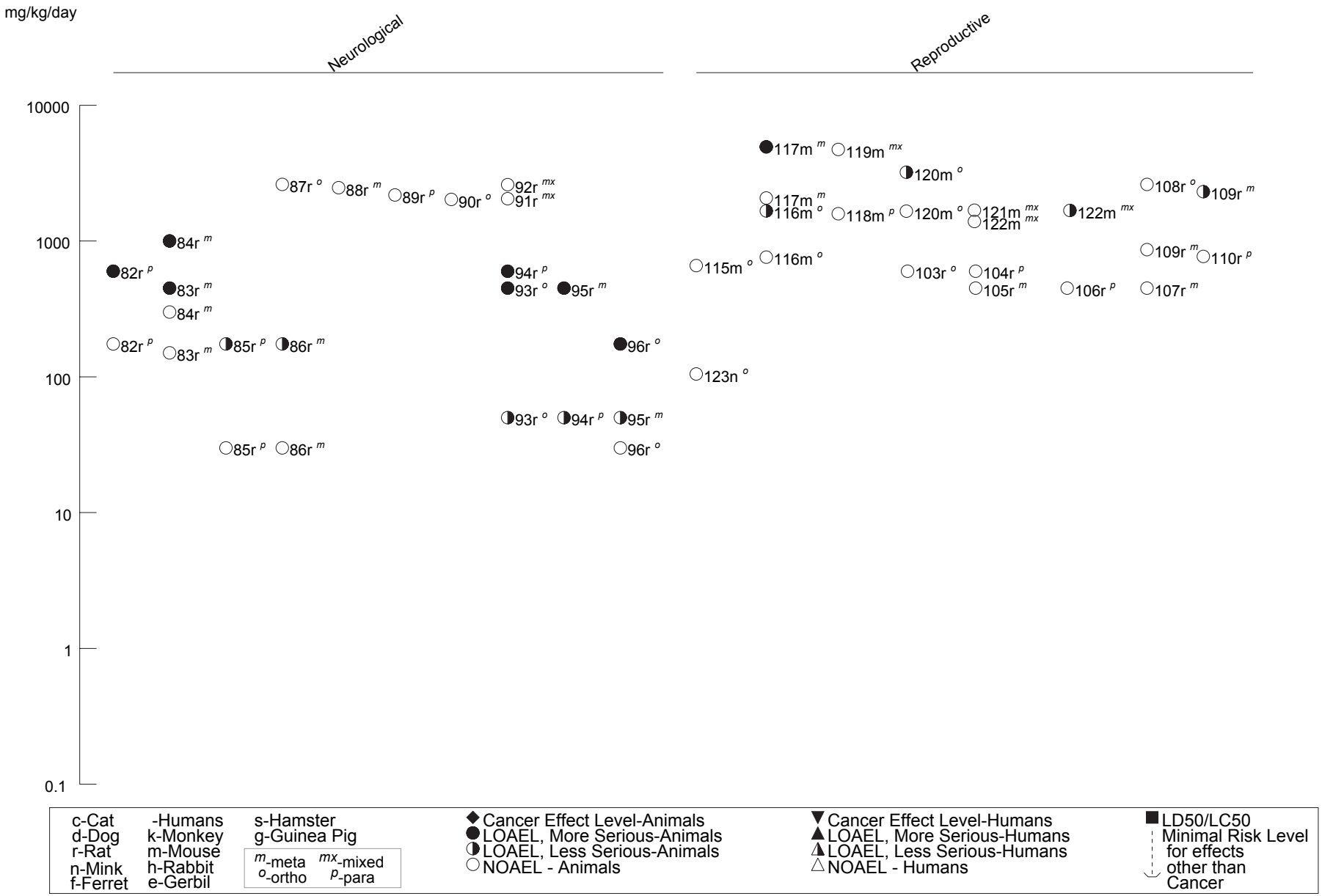


Figure 3-1 Levels of Significant Exposure to Cresols - Oral *(Continued)*

Intermediate (15-364 days)

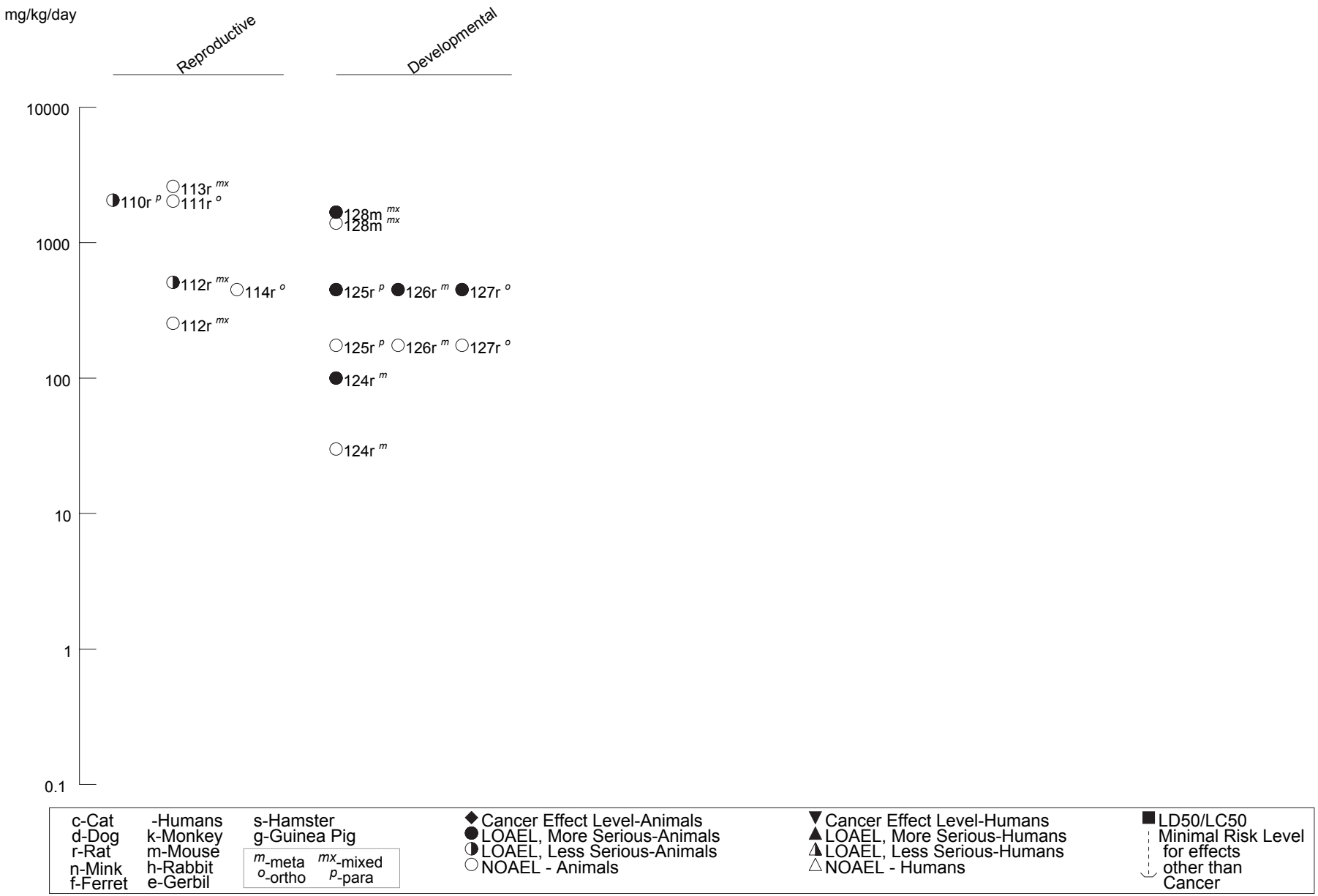
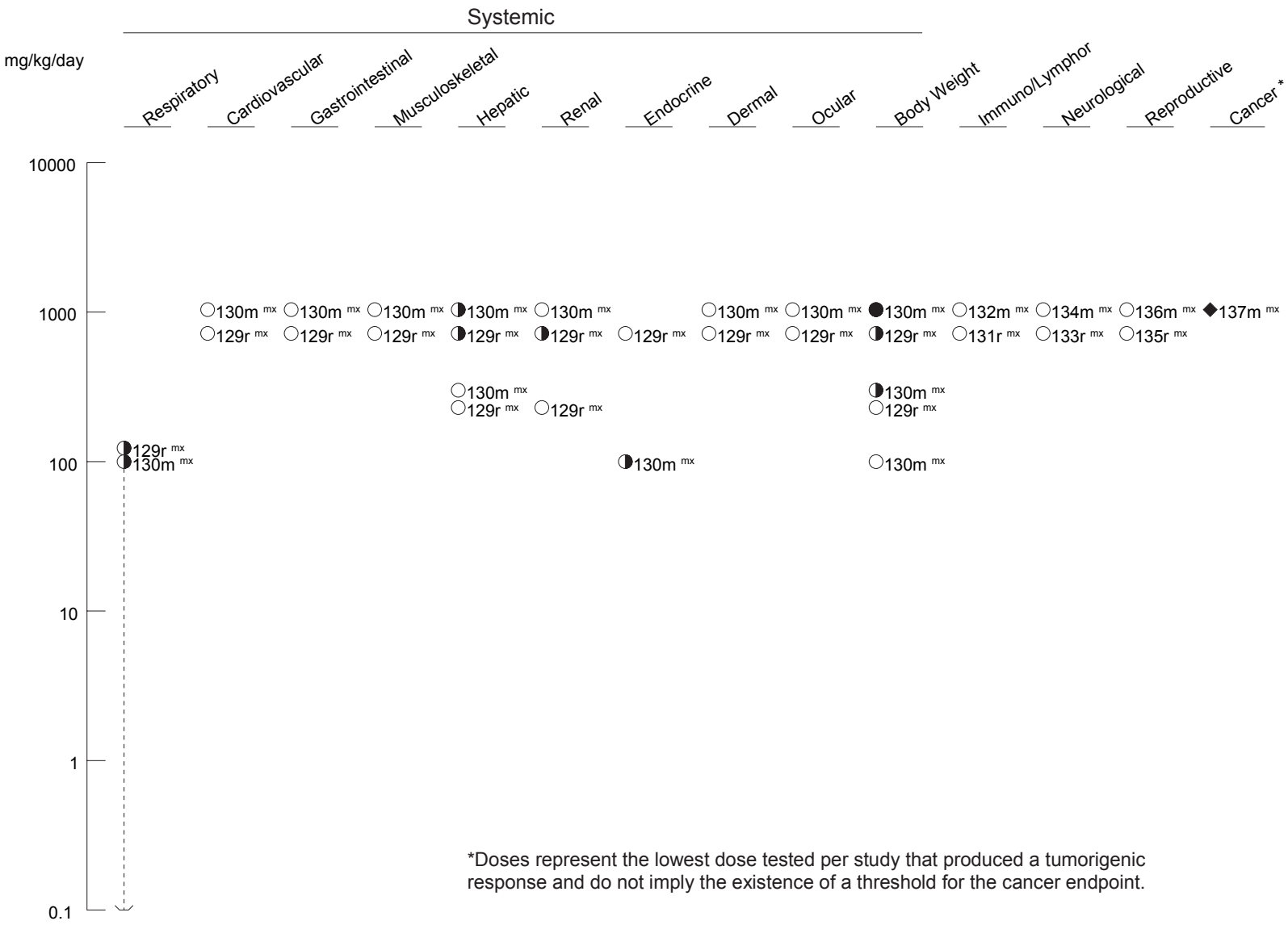


Figure 3-1 Levels of Significant Exposure to Cresols - Oral *(Continued)*

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat -Humans s-Hamster
d-Dog k-Monkey g-Guinea Pig
r-Rat m-Mouse
n-Mink h-Rabbit
f-Ferret e-Gerbil

m-meta *mx*-mixed
o-ortho *p*-para

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

$B6C3F_1$ mice also exhibited nasal changes following dietary treatment with *p*-cresol or the *m/p*-cresol mixture for 28 days (NTP 1992b). For *p*-cresol, the LOAEL in males and females was 163 and 207 mg/kg/day, respectively, with corresponding NOAELs of 50 and 60 mg/kg/day. For the mixture, the respective LOAELs in males and females were 4,530 and 604 with corresponding NOAELs of 1,490 and 200 mg/kg/day. Male mice dosed with 4,530 mg/kg/day of the cresol mixture also exhibited a significant increase in bronchiolar hyperplasia. In the 13-week study in mice with *o*-cresol and the cresol mixture, hyperplasia of the respiratory nasal epithelium was seen in males treated with 776 mg/kg/day, but not 402 mg/kg/day, and in females at 1,693 mg/kg/day, but not 923 mg/kg/day of the cresol mixture. No such lesions were seen in mice dosed with *o*-cresol in doses of up to 2,700–3,200 mg/kg/day for 13 weeks.

The respiratory system was also a target for *m/p*-cresol in male Fischer rats (females not tested) and female $B6C3F_1$ mice (males not tested) in a 2-year dietary study (NTP 2008). In rats, the response with the lowest threshold appeared to be hyperplasia of the respiratory epithelium of the nose, which occurred with an incidence of 3/50, 17/50, 31/50, and 47/50 in rats dosed with mean time-weighted average (TWA) doses of 0, 70, 320, and 720 mg/kg/day, respectively; severity was minimal to mild. The incidence in the low-dose group (17/50, 34%) was very similar to that reported in the 13-week study (NTP 1992b) (3/10, 30%) in male rats that received mean daily doses of 123 mg/kg/day during the 13 weeks of the study. Since the mean dose received by the low-dose rats during the first 13 weeks of the 2-year study was 123 mg/kg/day (from a table in the NTP report providing mean weekly doses during the first 13 weeks), it means that the lesions were already established by week 13 of the 2-year study and did not increase in severity. Therefore, the value listed as a LOAEL in the LSE table is 123 mg/kg/day, the true mean dose during the first 13 weeks, rather than the low TWA dose of 70 mg/kg/day for the entire duration of the chronic study. Other nasal lesions observed in rat included squamous metaplasia of the nasal epithelium, hyperplasia of the goblet cell, and inflammation of the nose. In mice, the most sensitive response was hyperplasia of the bronchiole of the lung, occurring with incidences of 0/50, 42/50, 44/49, and 47/50 in mice dosed with mean TWA doses of 0, 100, 300, and 1,040 mg/kg/day, respectively. Hyperplasia of the bronchiole of the lung was not a lesion reported in mice in the 13-week NTP (1992b) study. Dose-related elevated incidences of respiratory epithelium hyperplasia were also reported at 300 and 1,040 mg/kg/day in mice (NTP 2008). The LOAEL of 100 mg/kg/day for bronchiole hyperplasia in female mice exposed for 2 years was used to derive a chronic-duration oral MRL for cresols.

Pregnant rats (Tyl 1988b) and rabbits (Tyl 1988a) exposed to *o*-, *p*-, and *m*-cresol were reported to have audible respiration and labored breathing. These effects may be of a neurologic origin, rather than a direct effect on the respiratory system (Section 3.2.2.4).

Cardiovascular Effects. A woman who swallowed 500–750 mL of a concentrated cresol mixture exhibited tachycardia with polymorphic ventricular extra-systoles shortly after exposure (Labram and Gervais 1968). This was followed within 26 hours by ventricular fibrillation and cardiac arrest.

In rats exposed to *o*-cresol (EPA 1988b), *p*-cresol (EPA 1988c), or *m*-cresol (EPA 1988d) at levels up to 600 mg/kg/day for 13 weeks by gavage, histological examination of the heart revealed no changes that indicated an adverse effect on the heart. A 28-day dietary study reported no significant histopathological effects in the heart or aorta of rats dosed with up to approximately 2,600 mg/kg/day of each cresol isomer or with a mixture (58/41%) of *m*- and *p*-cresol (NTP 1992b). A similar lack of effects was reported in rats following 13 weeks of treatment with approximately 2,000 mg/kg/day of *o*-cresol or the cresol mixture in the diet (NTP 1992b).

In mice, treatment for 28 days with up to approximately 5,000 mg/kg/day of *o*-cresol, *m*-cresol, or the *m/p*-cresol mixture or 1,590 mg/kg/day of *p*-cresol had no significant effect on the gross or microscopic appearance of the heart or aorta (NTP 1992b). Similar effects were reported in mice dosed with up to 3,200 mg/kg/day of *o*-cresol or 1,693 mg/kg/day of the *m/p*-cresol mixture for 13 weeks (NTP 1992b). The data available suggest that the cardiovascular system is not a sensitive target for cresol toxicity.

No gross or microscopic alterations were observed in the heart of male rats and female mice administered mean doses of up to 720 and 1,040 mg/kg/day *m/p*-cresol, respectively, via the diet for 2 years (NTP 2008).

Gastrointestinal Effects. Mouth and throat burns, abdominal pain, and vomiting were common symptoms of cresol poisoning among 52 patients who drank between 4 and 120 mL of a disinfectant containing 25–50% mixed cresols (Isaacs 1922). These effects were also seen in a man who swallowed approximately 250 mL of a concentrated cresol mixture in a suicide attempt (Jouglard et al. 1971). Hemorrhagic degeneration of the pancreas was the cause of death in a woman who swallowed a disinfectant suspected of containing cresols. It was not clear, however, if this effect was actually produced by the disinfectant or was due to a pre-existing condition (little disinfectant was taken) (Dellal 1931). In a man who ingested an unknown amount of cresol, gastrointestinal endoscopy performed

10 hours later revealed dark red corrosive injuries on the esophagus and stomach wall (Hayakawa 2002). Diffuse erosions in the gastrointestinal tract have been observed in subjects who drank saponated cresol solutions containing about 50% cresol (Bruce et al. 1976; Kamijo et al. 2003; Wu et al. 1998; Yashiki et al. 1990).

Rats exposed to cresols in doses up to 600 mg/kg/day for 13 weeks by gavage in corn oil did not have gastrointestinal lesions (EPA 1988b, 1988c, 1988d). However, dietary administration of *p*-cresol in doses of approximately 1,415 mg/kg/day for 20 weeks produced an increased incidence of mild and moderate hyperplasia of the forestomach of hamsters (Hirose et al. 1986). Rats treated for 28 days with up to approximately 2,200–2,400 mg/kg/day of each cresol isomer in the diet showed no significant alterations in the gastrointestinal tract. However, doses ≥260 mg/kg/day of *m/p*-cresol mixture (58/41%) induced hyperplasia and hyperkeratosis of the esophageal epithelium in male and female rats (NTP 1992b); the NOAEL was 90–95 mg/kg/day. Higher doses (2,500–2,600 mg/kg/day) also induced hyperplasia in the epithelium of the forestomach. Longer treatments (13 weeks) with approximately 2,000 mg/kg/day of *o*-cresol or the cresol mixture had no significant effect on the gastrointestinal tract of rats (NTP 1992b).

In mice, doses of up to near 5,000 mg/kg/day of *o*-, *m*-, or an *m/p*-cresol mixture had no significant effect on the gastrointestinal tract (NTP 1992b). Similarly, no increased incidence of gastrointestinal tract lesions occurred with up to 1,590 mg/kg/day of *p*-cresol; the highest dietary dose of *p*-cresol was not estimated by NTP (1992b) since it killed all the mice, but was probably near 5,000 mg/kg/day. The 13-week studies in mice provided no evidence of gastrointestinal alterations following doses of approximately 1,500–1,700 mg/kg/day of the cresol mixture, but doses of 2,700–3,200 mg/kg/day of *o*-cresol induced minimal forestomach epithelial hyperplasia (NTP 1992b).

No gross or microscopic alterations were observed in the gastrointestinal tract of male rats and female mice administered mean doses of up to 720 and 1,040 mg/kg/day *m/p*-cresol, respectively, via the diet for 2 years (NTP 2008).

Hematological Effects. Hematological effects were described in four people who ingested cresol-containing products. One woman swallowed 100 mL of a disinfectant containing 50% mixed cresols, receiving a dose of approximately 1 g/kg (Chan et al. 1971). Methemoglobin was seen in the blood after 1.5 hours, but was no longer detected after 6 hours. Some Heinz bodies were observed after 6 hours, but these disappeared after 2 days. A second woman who drank 250 mL of disinfectant (roughly 2 g/kg) experienced more serious effects. Methemoglobinemia and markedly reduced glutathione levels were

seen after 7 hours. After 3 days, the patient developed severe hemoglobinemia and hemoglobinuria, indicating that massive intravascular hemolysis had occurred; extensive Heinz body formation had also taken place. The patient died the next day, apparently from thrombus formation and kidney failure secondary to acute intravascular hemolysis (Chan et al. 1971). A marked increased in methemoglobin also was observed in a man 15 hours after he swallowed a cresol solution of unknown concentration (Minami et al. 1990). Heinz body formation, hemoglobinemia, hemoglobinuria, and hemolytic anemia were also seen in a man who drank 100 mL of penetrating oil containing 12% mixed cresols, receiving a dose of about 170 mg/kg (Cote et al. 1984). In addition, a man who swallowed approximately 250 mL of a concentrated cresol mixture developed severe hemolytic anemia during the second week following ingestion (Jouglard et al. 1971). Isaacs (1922) did not find abnormalities in the blood of any of 52 patients who had ingested cresols, but the specific analyses performed were not reported. Low platelet count, which could have been due to disseminated intravascular congestion, was described in a man who drank an undetermined amount of cresol (Hayakawa 2002). Leukocytosis and hemolysis were reported in a man who drank 300 mL of a 50% saponated solution of cresols (Wu et al. 1998). The hematological effects of cresols appear to be due to both an oxidant effect on the cell contents and a direct effect on the red cell membrane (Chan et al. 1971).

Severe hematological effects, such as those reported in humans, were not observed in animals exposed to cresols possibly because acute high-dose studies in animals did not investigate hematological effects. Mild decreases in red blood cells, blood hemoglobin concentrations, and hematocrit were reported in rats dosed by gavage with 175 mg/kg of *p*-cresol for 13 weeks (EPA 1988c), but the effects were not produced by the other isomers (EPA 1988b, 1988d). Mild and inconsistent changes in red blood cell count seen in mink were of questionable significance (Hornshaw et al. 1986). A study in rats reported increased incidence of moderate bone marrow hypocellularity following 28 days of a diet that provided approximately 2,000–2,200 mg/kg/day of *p*-cresol or 2,500–2,600 mg/kg/day of an *m/p*-cresol mixture (NTP 1992b); the NOAELs were near 800 mg/kg/day. Blood parameters were not monitored in this 28-day study. Bone marrow hypocellularity also was reported in female rats treated with ≥1,021 mg/kg/day of *o*-cresol for 13 weeks and in male and female rats treated with approximately 2,100 mg/kg/day of *m/p*-cresol (NTP 1992b). Hematological parameters in the 13-week studies with both *o*-cresol and *m/p*-cresol were unremarkable, although there was a tendency to hemoconcentration in animals receiving the highest doses (>2,000 mg/kg/day) early in the study.

Male mice treated for 28 days with 4,530 mg/kg/day of *m/p*-cresol showed mild to moderate bone marrow hypocellularity, but no such effect was seen at 1,490 mg/kg/day or in females treated with up to

4,730 mg/kg/day (NTP 1992b). Bone marrow hypocellularity also was observed in all mice treated with the highest dietary level of *p*-cresol, 30,000 ppm (NTP did not estimate daily doses at this level since all mice died), but not at estimated doses near 1,500 mg/kg/day (NTP 1992b). No significant hematological effects were reported in mice in the 13-week study with *o*-cresol (2,700–3,200 mg/kg/day) or *m/p*-cresol (1,500–1,700 mg/kg/day).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following oral exposure to cresols.

Cresols had no effect on the incidence of gross or microscopic lesions in the muscle or bone of rats given doses up to 600 mg/kg/day by gavage for 13 weeks (EPA 1988b, 1988c, 1988d). The NTP (1992b) dietary studies examined sternebrae and femurs of rats and mice and found no significant gross or microscopic alterations in these tissues. Maximal doses of all the cresols tested were approximately 2,000–2,600 mg/kg/day in rats (28-day and 13-week studies), 4,500–5,000 mg/kg/day (28-day study in mice), 2,700–3,200 mg/kg/day (13-week in mice with *o*-cresol), and 1,500–1,600 mg/kg/day (13-week in mice with *m/p*-cresol). Skeletal muscle was not examined in the NTP (1992b) study. No gross or microscopic alterations were observed in bone (not specified) of male rats and female mice administered mean doses of up to 720 and 1,040 mg/kg/day *m/p*-cresol, respectively, via the diet for 2 years (NTP 2008).

Hepatic Effects. Moderate fatty degeneration was found in the liver of a woman who died after drinking 250 mL of a disinfectant, which contained 50% mixed cresols (Chan et al. 1971). The liver appeared normal in another woman who died after ingesting a disinfectant suspected of containing cresols (Dellal 1931). In a more recent case report, a woman who ingested 70 mL of a 50% cresol solution experienced a marked increase in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities (more than 100-fold increase) after a 24-hour asymptomatic period (Hashimoto et al. 1998). The hepatocellular injury was not severe enough to cause liver descompensation and there was no evidence of hepatic encephalopathy. Blood work done 22 days after the poisoning episode revealed normal serum AST and ALT values. Similar results have been reported in other cases of acute oral intoxication with cresols (Bruce et al. 1976; Hayakawa 2002; Kamijo et al. 2003).

Following oral exposure of animals to cresols by gavage, increased relative liver weight and increased serum transaminase levels were reported. Relative liver weights in rats increased following gavage exposure to doses of 450 mg/kg/day of cresols during pregnancy (Tyl 1988a). Longer-term exposure to

levels as low as 5 mg/kg/day had the same effect in mink and ferrets (Hornshaw et al. 1986). However, in these studies, changes in liver weight were not accompanied by histological changes and may not have indicated adverse effects. Increased levels of serum AST and ALT were seen in female rats given 600 mg/kg/day of *p*-cresol by gavage for 13 weeks and appeared to be correlated with the presence of hepatic inflammation (EPA 1988c).

Dietary administration of approximately ≥700–800 mg/kg/day of *o*-, *m*-, or *m/p*-cresol to rats for 28 days resulted in increases (>10%) in absolute and relative liver weight (NTP 1992b). The NOAELs were approximately 260–270 mg/kg/day. For *p*-cresol, doses of 242 mg/kg/day caused a 16% increase in absolute liver weight, whereas 83 mg/kg/day produced an increase of only 6%. No significant gross or microscopic changes were seen in the liver in this series of experiments. In the 13-week rat study with *o*-cresol, absolute and relative liver weights were increased in males and females at ≥510 mg/kg/day. Clinical chemistry tests showed an increase in serum bile acids in females at ≥1,021 mg/kg/day and in males at 2,028 mg/kg/day. However, there was no indication of liver necrosis or cholestasis, as serum ALT, 5'-nucleosidase, and alkaline phosphatase activities were not significantly affected. Furthermore, there were no gross or histological alterations in the liver even with the highest doses of 2,028 mg/kg/day. Similar results were reported for the *m/p*-cresol mixture. Clinical chemistry tests showed some alterations in enzymes activities, but no clear pattern or dose-relationships. Bile acids in serum were increased at study termination in females at 2,050 mg/kg/day and in males at 241 and 991 mg/kg/day. Gross necropsy and histopathology of the liver did not reveal any significant treatment-related alterations. Administration of mean doses of 720 mg *m/p*-cresol mixture/kg/day for 2 years male Fisher rats produced a significant increase in the incidence of eosinophilic foci in the liver of (NTP 2008). In rats dosed with ≤230 mg/kg/day, the incidences were comparable to controls.

In mice, treatment in the diet with up to 5,000 mg/kg/day (the highest dose tested) of *o*- or *m*-cresol for 28 days caused mortality but did not induce significant histopathological effects on the liver (NTP 1992b). Doses of 1,590 mg/kg/day of *p*-cresol increased absolute and relative liver weight (15–20%) in female mice, but caused no histopathology; no significant changes were seen at 564 mg/kg/day. Mice treated with a higher dose level of *p*-cresol (30,000 ppm in food, but doses were not estimated by NTP) that killed 9/10 mice by day 5 showed liver necrosis. The *m/p*-cresol mixture, at ≥1,880 mg/kg/day, increased absolute and relative liver weight in female mice, but there were no histological alterations even at the higher dose level of 4,730 mg/kg/day. In the 13-week study, *o*-cresol increased liver weight in males at ≥1,723 mg/kg/day, whereas the *m/p*-cresol mixture had the same effect at ≥776 mg/kg/day (NTP 1992b). There were no treatment-related alterations in liver morphology in the 13-week study or in

clinical chemistry tests that would have indicated alterations in liver function. The only effect reported in female mice in the 2-year NTP (2008) bioassay with *m/p*-cresol was an increased incidence of eosinophilic foci in the liver at the 1,040 mg/kg/day dose level, but not at ≤300 mg/kg/day.

While some hepatic parameters were affected by treatment with some cresol isomers, the overall database does not suggest that the liver is a particularly sensitive target for cresol toxicity.

Renal Effects. Massive eosinophilic necrosis was found in the proximal tubule of a woman who died after drinking 500–750 mL of a concentrated cresol mixture (Labram and Gervais 1968). This effect was considered by the investigators to have occurred before death, and may have been due to the toxic action of cresol. Renal effects in a woman who drank 250 mL of a disinfectant (50% mixed cresols), and later died, consisted of fibrin clumps in the glomeruli and a moderate level of tubular degeneration, which could have been due to intravascular thrombosis (Chan et al. 1971). Mild congestion of the kidney was reported in a second woman who died following consumption of a disinfectant suspected of containing cresols (Dellal 1931). Greatly elevated blood urea nitrogen (BUN) and serum creatinine were reported in another case of ingestion of a saponated cresol solution (Wu et al. 1998). Among 52 patients with diagnosed cresol poisoning, there were signs of renal toxicity, including darkly colored urine, renal irritation, and in a few cases, reduced phenolsulphonephthalein output (Isaacs 1922). Bruce et al. (1976) observed lipofuscin deposits in the cells of many of the proximal convoluted tubules in a woman who died 2 hours after ingestion of an unknown quantity of Lysol®.

Exposure of male rats to 600 mg/kg/day by gavage for 13 weeks induced a slight increase, which did not appear to be dose related, in the incidence of histological changes characteristic of chronic nephropathy (EPA 1988c). No such changes were seen in rats treated with comparable doses of *o*- or *m*-cresol and urinalyses provided no evidence for altered kidney function with any of the cresol isomers. Exposure of rats to *m*-, *p*-, or an *m/p*-cresol mixture in the diet for 28 days in doses of up to 2,200–2,600 mg/kg/day did not induce treatment-related alterations in gross or microscopic appearance of the kidneys (NTP 1992b). Doses of ≥861 mg/kg/day of *o*-cresol increased absolute and relative kidney weight (13–15%) in male rats, whereas 266 mg/kg/day produced changes in kidney weight of ≤5% relative to controls. Kidney weight in females was not significantly altered. Histological examination of the kidneys did not reveal lesions. The 13-week study found no renal alterations in rats dosed with up to approximately 2,000 mg/kg/day of *o*-cresol or the *m/p*-cresol mixture (NTP 1992b). In both cases, urinalyses provided no evidence of renal injury. Increased incidence of transitional epithelium hyperplasia (minimal to mild severity) of the renal pelvis (8/50 compared with 0/50 in controls) was reported in male rats that received

mean doses of 720 mg *m/p*-cresol/kg/day for 2 years through the diet (NTP 2008); the NOAEL was 230 mg/kg/day.

Renal effects in mice in the NTP (1992b) studies were limited to kidney necrosis, which was observed in mice that died after being exposed to a diet containing 30,000 ppm *p*-cresol (dosed were not calculated by NTP, but were probably in the range of 4,000–5,000 mg/kg/day). *p*-Cresol in doses of 1,590 mg/kg/day had no significant effect on the kidneys in the 28-day study. The other isomers and the *m/p*-cresol mixture did not induce adverse kidney effects in doses of up to 4,000–4,500 mg/kg/day and neither did *o*-cresol (2,700–3,200 mg/kg/day) or *m/p*-cresol (1,500–1,700 mg/kg/day) in the 13-week study. No significant gross or microscopic alterations were reported in the kidneys from female mice dosed with up to 1,040 mg *m/p*-cresol in the diet for 2 years (NTP 2008).

The available studies in animals do not suggest that the kidneys are a sensitive target for cresol toxicity.

Endocrine Effects. No studies were located regarding endocrine effects in humans following oral exposure to cresols.

Studies in animals do not suggest that endocrine organs are susceptible targets for cresol toxicity. A 13-week gavage study with the three cresol isomers reported no treatment-related gross or microscopic alterations in the pituitary, thyroid, adrenals, and pancreas of rats treated with doses of up to 450 mg/kg/day of *m*-cresol or 600 mg/kg/day of *o*- and *p*-cresol (EPA 1988b, 1988c, 1988d).

Both the 28-day and 13-week dietary studies with cresol isomers and a cresol mixture conducted by NTP (1992b) examined the adrenals, pancreas, thyroid, parathyroid, and pituitary of rats and mice. The only treatment-related effect observed was an increase in colloid within the thyroid gland follicles in rats treated with an *m/p*-cresol mixture for 28 days and 13 weeks. The LOAEL and NOAEL in the 28-day were approximately 270 and 90 mg/kg/day, respectively, in males and females. In the 13-week study, the LOAEL for females was 509 mg/kg/day and for males 991 mg/kg/day; the corresponding NOAELs were 254 and 486 mg/kg/day. NTP (1992b) noted that the biological significance of the lesions is uncertain because it was not seen with the individual isomers, nor was it associated with follicular cell hypertrophy and/or hyperplasia. The highest doses of the individual isomers tested in the rats were in the range of 2,000–2,400 mg/kg/day. Mice treated for 28 days received doses of up to 5,000 mg/kg/day of cresols. Mice treated for 13 weeks received up to 3,200 mg/kg/day of *o*-cresol and 1,700 mg/kg/day of *m/p*-cresol. Administration of up to 720 mg *m/p*-cresol/kg/day to male rats via the diet for 2 years did not cause any

significant alteration in gross or microscopic appearance of the pancreas or of the adrenal, pituitary, parathyroid, and thyroid glands (NTP 2008). In female mice, administration of *m/p*-cresol for 2 years induced a significant increase in the incidence of mild follicular degeneration of the thyroid in all dosed groups (7/48, 24/48, 24/49, and 21/50 in the 0, 100, 300, and 1,040 mg/kg/day dose groups, respectively) (NTP 2008). The LOAEL of 100 mg/kg/day for mild follicular degeneration of the thyroid gland in female mice was used to derive a chronic oral MRL for cresols.

Dermal Effects. No studies were located regarding dermal effects in humans following oral exposure to cresols.

There were no gross or histological alterations in the skin of rats treated with cresol isomers for 28 days or 13 weeks in doses of 2,100–2,600 mg/kg/day (NTP 1992b). In mice, the only significant treatment-related effect was alopecia in males and females treated with 4,530 and 4,730 mg/kg/day, respectively, of *m/p*-cresol for 28 days. No such effect occurred in mice treated with up to 3,205 mg/kg/day of *o*-cresol or 1,693 mg/kg/day of *m/p*-cresol for 13 weeks. No exposure-related histopathological changes in the skin were observed in rats and mice exposed up to 720 or 1,040 mg/kg/day, respectively, *m/p*-cresol in the diet for 2 years (NTP 2008).

Ocular Effects. No studies were located regarding ocular effects in humans following oral exposure to cresols.

Pregnant rabbits repeatedly given ≥50 mg/kg/day of the cresol isomers during gestation were found to have significant amounts of ocular discharge, some of which may have been due to hemorrhaging (Tyl 1988b), but no gross or microscopic lesions of the eye were found in rats given cresols in doses of up to 450 mg/kg/day of *m*-cresol or 600 mg/kg/day of *o*- or *p*-cresol by oral gavage for 13 weeks (EPA 1988b, 1988c, 1988d; TRL 1986). No exposure-related histopathological changes in the eye were observed in rats and mice exposed up to 720 or 1,040 mg/kg/day, respectively, *m/p*-cresol in the diet for 2 years (NTP 2008).

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

In animals, a common response to oral exposure to cresols, particularly in oral gavage studies, was decreased growth, often associated with decreased food consumption (EPA 1988b, 1988c, 1988d;

Hornshaw et al. 1986; Koizumi et al. 2003; Neeper-Bradley and Tyl 1989a, 1989b; TRL 1986; Tyl 1988a; Tyl and Neeper-Bradley 1989). The effects were usually more pronounced during the early stages of the studies and, in almost all cases, were associated with significant reductions in food consumption. It should be mentioned also that the dose levels that reduced food consumption and body weight gain induced neurological effects such as hypoactivity, incoordination, and tremors. Reduced body weight gain was also observed in the dietary studies in rats and mice, generally at the highest dose levels tested (i.e., ≥2,000 mg/kg/day) and was almost always associated with reduced food consumption (NTP 1992b). Whether the latter is due to poor palatability or other reason is unknown since pair-fed groups were not utilized.

Final body weight in male rats treated with 720 mg *m/p*-cresol/kg/day in the diet for 2 years was 15% lower than in controls (NTP 2008), the NOAEL was 230 mg/kg/day. In the same study, final body weight of female mice dosed with 300 and 1,040 mg *m/p*-cresol/kg/day was reduced 11 and 24%, respectively, relative to controls. Food consumption was not significantly affected in either species throughout the study.

Metabolic Effects. Marked metabolic acidosis (pH 7.058) was reported in a man who drank an undetermined amount of cresol (Hayakawa 2002). Similar observations were made by Kamijo et al. (2003) in a man who drank about 150 mL of a saponated cresol solution containing about 50% cresol. No explicit mention of adverse metabolic effects was made in other reports of ingestion of cresols.

There is no evidence that cresols induced metabolic effects at the doses tested in the animal studies available.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans following oral exposure to cresols.

The only immunological end points examined in animal studies were weight and gross and microscopic appearance of the spleen and thymus and occasionally, lymph nodes. Spleen weight was unaffected by 28-day exposure to *o*-cresol in the feed at doses up to 400–720 mg/kg/day in ferrets and 320–480 mg/kg/day in mink (Hornshaw et al. 1986). Similarly, no effect was seen on spleen weight in a reproduction study in which mink were exposed to 105–190 mg/kg/day of *o*-cresol in the feed for 6 months (Hornshaw et al. 1986). Absolute spleen weight was decreased (approximately 18%) in male

rats given 600 mg/kg/day of *p*-cresol by gavage for 13 weeks, but relative spleen weight was unaffected and no lesions were found; neither weight nor morphological appearance of the thymus or mandibular lymph nodes was significantly altered (EPA 1988c). No significant alterations were seen in these tissues in rats given similar doses of *o*- or *m*-cresol (EPA 1988b, 1988d). Studies in rats and mice exposed to cresol isomers and a mixture of *m*- and *p*-cresol for 28 days or 13 weeks also found no significant histological alterations in lymphoreticular organs and tissues (NTP 1992b). Maximal doses in mice were near 5,000 mg/kg/day and in rats near 2,600 mg/kg/day. Similar results were reported in the 2-year study with maximal doses of *m/p*-cresol of 720 mg/kg/day in male rats and 1,040 mg/kg/day in female mice (NTP 2008). None of the studies mentioned above conducted tests of immunocompetence.

These NOAELs for lymphoreticular effects are presented in Table 3-1 and plotted in Figure 3-1.

3.2.2.4 Neurological Effects

Neurological effects have frequently been noted following oral exposure to cresols. A woman who drank approximately 100 mL of a disinfectant, which consisted of roughly 50% mixed cresols, was semiconscious after 2 hours. A second woman, who swallowed about 250 mL of the same disinfectant, was in a deep coma after 2 hours. She regained consciousness 10 hours later (Chan et al. 1971). A woman who swallowed 500–750 mL of a concentrated cresol mixture fell into a deep coma within 1 hour (Labram and Gervais 1968). Coma was a common feature of cresol poisoning among 52 patients studied by Isaacs (1922). The author noted that unconsciousness could occur very soon after exposure and could last 14 hours or more.

A series of neurological effects, including hypoactivity and lethargy, excess salivation, dyspnea, incoordination, muscle twitches and tremors, convulsions, and coma, have been reported in animals acutely exposed to cresols by gavage (Deichmann and Witherup 1944; Hornshaw et al. 1986; TRL 1986; Tyl 1988a, 1988b). The lowest dose at which neurological effects were reported was 50 mg/kg/day, which produced hypoactivity and labored respiration in pregnant female rabbits repeatedly dosed with *o*- or *p*-cresol during gestation (Tyl 1988b). In rats, effects such as hypoactivity and rapid labored respiration were seen at 50 mg/kg/day for all three isomers (TRL 1986). More serious effects, such as convulsions, were seen at 450 mg/kg/day or higher (TRL 1986).

A detailed oral neurotoxicity study of intermediate duration was performed on rats using all three cresol isomers administered by gavage for 13 weeks (TRL 1986). A host of clinical observations indicative of

neurotoxicity (including hypoactivity, rapid labored respiration, excessive salivation, and tremors) was reported at doses of 50 mg/kg/day or higher for all three isomers. However, the results of a number of neurobehavioral tests designed to assess demeanor and motor and reflex activity (testing was done 6 times throughout the 13 weeks prior to dosing) showed only sporadic differences with controls and/or alterations were not dose-related. No brain weight changes or histopathologic lesions in the brain or other nervous tissues were found for any isomer. Convulsions were reported at 450 mg/kg/day or higher (TRL 1986). More recently, salivation and tremors were reported in young rats treated by gavage with 1,000 mg/kg/day *m*-cresol, but not 300 mg/kg/day, for 28 days (Koizumi et al. 2003). Other studies of prolonged oral exposure to cresols by gavage had similar findings (EPA 1988b, 1988c, 1988d; Hornshaw et al. 1986; Neeper-Bradley and Tyl 1989a, 1989b; Tyl and Neeper-Bradley 1989). The only intermediate-duration gavage studies to determine NOAEL values for neurological effects were the two-generation reproduction studies in rats (Neeper-Bradley and Tyl 1989a, 1989b; Tyl and Neeper-Bradley 1989). Neurological NOAEL values of 30 mg/kg/day were reported for all three cresol isomers in these studies. However, tests for neurobehavioral effects were not performed. None of the studies mentioned above observed treatment-related gross or microscopic alterations in the brain, spinal cord, or sciatic nerve.

In the intermediate-duration dietary studies in rats and mice conducted by NTP (1992b), the most common adverse clinical signs of neurological impairment observed were lethargy and occasionally tremors, and were seen only in mice. Male and female mice dosed with 4,400–5,000 mg/kg/day of *o*-cresol for 28 days showed lethargy and tremors; these signs were not seen at 1,700 mg/kg/day. Female mice, but not males, exposed to 2,080 mg/kg/day of *m*-cresol for 28 days also exhibited lethargy. Lethargy was also seen in male mice dosed with 1,410 mg/kg/day of *p*-cresol and in male and female mice dosed with 4,530–4,730 mg/kg/day of the *m/p*-cresol mixture. These results indicate that, at least for the end points of lethargy and tremors, mice are more sensitive than rats. Gross and microscopic examination of the brain of rats and mice in the NTP (1992b) study did not reveal any treatment-related lesions. Similar negative observations were reported in male rats and female mice dosed with up to 720 and 1,040 mg/kg/day *m/p*-cresol, respectively, in the diet for 2 years (NTP 2008).

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.5 Reproductive Effects

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

Developmental toxicity studies in which pregnant rats (Tyl 1988a) and rabbits (Tyl 1988b) were exposed to cresols by gavage during gestation reported no effects on the reproductive parameters investigated (e.g., number of ovarian corpora lutea, number of implantation sites, number of viable fetuses), even at maternally toxic doses. Two-generation reproduction studies in rats (up to 450 mg/kg/day of each isomer by gavage) and mink (up to 105 mg/kg/day dietary *o*-cresol for 6 months) also failed to detect adverse effects on reproductive function or lesions in reproductive tissues (Hornshaw et al. 1986; Neeper-Bradley and Tyl 1989a, 1989b; Tyl and Neeper-Bradley 1989). These studies also included doses producing maternal toxicity. No histopathological lesions and only mild organ weight changes of doubtful significance were reported in the reproductive organs of animals exposed to up to 600 mg/kg/day of cresols by gavage for 13 weeks (EPA 1988b, 1988c, 1988d).

The NTP (1992b) study evaluated changes in weight and histopathology of reproductive organs of males and females, as well as sperm parameters and duration of the estrous cycle, of Fisher-344 rats and $B6C3F_1$ mice exposed via the diet to cresol isomers and to a mixture of *m*- and *p*-cresol. The only significant effects observed in rats in 28-day experiments included mild to moderate uterine atrophy in females dosed with 2,310 mg/kg/day of *m*-cresol or 2,060 mg/kg/day of *p*-cresol. In the 13-week study, doses of ≥509 of *m/p*-cresol lengthened the estrous cycle in females and doses of 1,024 and 2,050 mg/kg/day induced minimal to mild uterine atrophy. No significant effects were seen in male rats dosed with up to 2,200–2,600 mg/kg/day of cresols. In mice, 28 days of dosing with 1,670 mg/kg/day of *o*-cresol produced mild atrophy of the uterus, whereas 4,940 mg/kg/day of *m*-cresol induced mild to moderate atrophy of the mammary glands, uterus, and ovaries. Neither *p*-cresol nor the *m/p*-cresol mixture adversely affected the reproductive end points in mice in the 28-day study. A 13-week regimen of 3,205 mg/kg/day of *o*-cresol lengthened the estrous cycle in mice, and doses of up to 1,500–1,700 mg/kg/day of *m/p*-cresol did not induce any significant alterations in males or females. Treatment of male rats and female mice with up to 720 and 1,040 *m/p*-cresol/kg/day, respectively, in the diet for 2 years did not induce any significant alterations in the gross or microscopic morphology of reproductive organs (NTP 2008).

Two studies have evaluated the effects of *o*-cresol and a mixture of *m/p*-cresol on reproductive function end points in CD-1 mice using a continuous breeding protocol (NTP 1992a, 1992c). End points evaluated

included fertility, mean number of litters per pair, live litter size, weight and histopathology of reproductive organs, vaginal cytology, and sperm parameters. Both studies started with a 14-week cohabitation period in which males and females received the test material in the diet. The highest doses during this period were 660 mg/kg/day for *o*-cresol and 1,682 mg/kg/day for *m/p*-cresol. No significant alterations were observed with *o*-cresol at any stage of the study. However, the highest dose of *m/p*-cresol significantly decreased the number of live pups/litter and increased the cumulative days to litter; a dose level of 1,390 mg/kg/day was a NOAEL. To determine which sex was the affected sex during the cohabitation period, a 1-week crossover mating trial was conducted, but the results indicated that either sex could have been affected. In neither study was fertility affected. In addition, sperm parameters and gross and microscopic morphology of reproductive organs were not affected by treatment with the cresols.

NOAEL and LOAEL values for reproductive effects derived from these studies are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.6 Developmental Effects

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

Developmental effects have been reported in animals given cresols, but only at maternally toxic doses. Maternal effects in rats dosed by gavage on gestation days 6–15 (audible respiration, reduced body weight gain, reduced food consumption, ataxia, tremors, and hypoactivity) occurred at 450 mg/kg/day (Tyl 1988a). At this dose, both *o*- and *p*-cresol produced slight fetotoxicity (increased incidences of dilated lateral ventricles in the brain and minor skeletal variations, respectively), but had no effect on malformation incidence or gestation parameters (e.g., the number of implantations per litter or fetal body weight per litter). No effects of any kind were seen at lower doses. *m*-Cresol had no effect on gestation parameters, fetotoxicity, or the incidence of malformations, even at maternally toxic doses (Tyl 1988a). An additional study in which rats were dosed only on gestation day 11 with up to 1,000 mg/kg of *p*-cresol reported no significant effects on post-implantation loss, litter size, viability, or postnatal weight of the offspring, even when maternal toxicity was evident at doses ≥410 mg/kg (Kavlock 1990). Slight maternal toxicity in the form of decreased weight gain was also observed at the 1,682 mg/kg/day dose level. In rabbits dosed on gestation days 6–18 with up to 100 mg/kg/day of each isomer, maternal effects, such as audible respiration, ocular discharge, and hypoactivity, were seen following exposure to *o*- or *p*-cresol at 50 mg/kg/day (Tyl 1988b). At 100 mg/kg/day, *o*-cresol produced slight fetotoxicity (increased incidences

of subepidermal hematoma on the head and poorly ossified sternebrae), but no other effects at any dose. Neither *p*- nor *m*-cresol produced any developmental effects in this study (Tyl 1988b).

Fetotoxicity was also observed at parentally-toxic doses in two-generation reproduction studies. Rats treated by gavage with 450 mg/kg/day of *o*- and *p*-cresol for 10 weeks before mating produced F_1 offspring that had reduced body weight 4–6 weeks after birth. This dose also produced overt toxicity in the parents (Neeper-Bradley and Tyl 1989a; Tyl and Neeper-Bradley 1989). In contrast to the results of the developmental toxicity studies discussed above, *m*-cresol was the most potent developmental toxicant among the cresols in the two-generation studies. This isomer reduced pup survival during lactation when administered by gavage at the high dose of 450 mg/kg/day (Neeper-Bradley and Tyl 1989b). Parental toxicity manifested as reduced body weight gain was reported at the low dose of 30 mg/kg/day. Decreased number of live pups/litter (F_1) was reported in a 2-generation reproductive study in mice exposed to 1,682 mg/kg/day of an *m/p*-cresol mixture for 14 weeks, but not at 1,390 mg/kg/day (NTP 1992c).

The comparative susceptibility of newborn and young rats to *m*-cresol was studied by Koizumi et al. (2003). Neonates were treated by gavage with up to 300 mg/kg/day *m*-cresol from postnatal day 4 to 21, whereas 5-week-old rats were dosed with up to 1,000 mg/kg/day for 28 days. Most neonates exhibited deep respiration, hypersensitivity on handling, and tremors under contact stimulus at 300 mg/kg/day. Final body weight also was significantly reduced at this dose level. Tremors also occurred in few neonates at 100 mg/kg/day, but no clinical signs were seen at 30 mg/kg/day. No significant alterations were reported in clinical chemistry, hematology, gross or microscopic pathology (major organs and tissues), or physical development and sexual maturation. In the young rats, clinical signs such as salivation, tremors, and reduced weight gain were observed at 1,000 mg/kg/day, but there were no significant alterations in clinical chemistry, hematology, or histopathological changes at this dose level. A dose level of 300 mg/kg/day *m*-cresol was a NOAEL in 5-week-old rats, whereas 30 mg/kg/day was a NOAEL in neonates.

NOAEL and LOAEL values derived from these studies are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.7 Cancer

No studies were located regarding cancer in humans following oral exposure to cresols.

In an intermediate-duration study, a diet that provided approximately 1,415 mg/kg/day of *p*-cresol for 20 weeks produced an increased incidence of mild to moderate forestomach hyperplasia in hamsters, suggesting that this cresol isomer may have the potential to act as a promoter of forestomach carcinogenesis in this species (Hirose et al. 1986). However, promotion potential was not tested directly. However, *p*-cresol did not produce forestomach hyperplasia in rats treated with the chemical in the diet (2% or approximately 2,140 mg/kg/day) for an unspecified period of time (Altmann et al. 1986), but rats are generally less sensitive than hamsters to inducers of forestomach lesions. In mice, simultaneous administration of 1 mg of *o*-cresol and 1 mg of benzo[a]pyrene twice daily by gavage for up to 30 weeks increased the incidence and malignancy of forestomach tumors and shortened their latency relative to benzo[a]pyrene alone (Yanysheva et al. 1993). However, administration of *o*-cresol before or after benzo[a]pyrene decreased the carcinogenicity of the latter substance.

A recently conducted 2-year feeding study with a mixture of *m*- and *p*-cresol (60%/40%) found no evidence of neoplastic effects in male Fischer-344 rats (females were not tested) that received mean doses of up to 720 mg/kg/day of the test material (NTP 2008). However, NTP (2008) determined that a slight nonstatistically significant increase ($p=0.121$) in the incidence of renal tubule adenoma constituted an equivocal finding. In female $B6C3F_1$ mice (males were not tested) that received mean doses of approximately 0, 100, 300, or 1,040 mg/kg/day, the incidence of squamous cell papilloma of the forestomach was significantly increased ($p<0.001$) in the high dose group (0/50, 1/50, 1/49, 10/50). No other significant neoplastic effect was reported in mice.

The EPA (IRIS 2008) has classified the three cresol isomers in Group C, “possible human carcinogens,” based on inadequate human data and limited data in animals (the assessment is dated 10/89). The assessment was based on an increased incidence of skin papillomas in mice in an initiation-promotion study and on the fact that the cresol isomers produced positive results in genetic toxicity studies both alone and in combination. Based on updated guidelines for carcinogen assessment (EPA 2005c), cresols fall in the category of chemicals for which there is “inadequate information to assess carcinogenic potential.” EPA did not derive quantitative estimates of carcinogenic risk for cresols (IRIS 2008). EPA’s assessment of cresols’ carcinogenicity was conducted before the results of the NTP (2008) study became available.

3.2.3 Dermal Exposure

3.2.3.1 Death

There are two case reports of people who died following dermal exposure to cresols. In one case, a 1-year-old baby had 20 mL of a cresol derivative (90% mixed cresols in water) spilled on his head, covering about 7% of his body surface. The baby died in coma within 4 hours (Green 1975). Assuming the baby weighed approximately 10 kg, the lethal dose in this case can be estimated to have been roughly 2 g/kg if all the cresol was absorbed, but was probably less since the infant's head was washed with soap and water 5 minutes after the spill. In the other case, a man fell into a vat of a cresylic acid derivative (cresol content unknown) and suffered burns on 15% of the body surface. Anuria was evident after 36 hours and blood urea content rose steadily during the following days. The patient fell into a coma on the 9th day, and death occurred on the 10th day (Cason 1959). Dermal absorption of cresol also appears to have been responsible for the death of a man who worked with an antiseptic solution containing concentrated mixed cresols for 2 days prior to becoming ill (Larcan et al. 1974).

In rabbits, dermal LD_{50} values for cresols were 890, 300, 2,830, and 2,000 mg/kg for *o*-, *p*-, *m*-, and mixed cresols, respectively (Vernot et al. 1977). These values are recorded in Table 3-2. Based on these LD_{50} values, *p*-cresol appears to be more toxic dermally than *o*-cresol, with *m*-cresol being the least toxic of the three isomers.

3.2.3.2 Systemic Effects

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

Respiratory Effects. Hemorrhagic pulmonary edema was found at necropsy in a 1-year-old baby who died after having 20 mL of a cresol-containing product spilled on his head (Green 1975). Liu et al. (1999) reported a case of a woman who suffered acute respiratory failure following chemical burns caused by skin contact with a saponated solution of mixed cresols.

No studies were located regarding respiratory effects in animals following dermal exposure to cresols.

Gastrointestinal Effects. No lesions were found in the gastrointestinal tract of a 1-year-old baby who died after dermal exposure to a cresol-containing product (Green 1975).

Table 3-2 Levels of Significant Exposure to Cresols - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
ACUTE EXPOSURE								
Death								
Rabbit	1 d 24 hr/d				2000 mg/kg/day	(LD50)	Vernot et al. 1977 mix	
Rabbit	1 d 24 hr/d				890 mg/kg/day	(LD50)	Vernot et al. 1977 ortho	
Rabbit	1 d 24 hr/d				2830 mg/kg/day	(LD50)	Vernot et al. 1977 meta	
Rabbit	1 d 24 hr/d				300 mg/kg/day	(LD50)	Vernot et al. 1977 para	
Systemic								
Rabbit	1 d 4 hr/d	Dermal			147 mg/kg/day	(skin corrosion)	Vernot et al. 1977 mix	
Rabbit	1 d 4 hr/d	Dermal			147 mg/kg/day	(skin corrosion)	Vernot et al. 1977 ortho	
Rabbit	1 d 4 hr/d	Dermal			147 mg/kg/day	(skin corrosion)	Vernot et al. 1977 meta	
Rabbit	1 d 4 hr/d	Dermal			147 mg/kg/day	(skin corrosion)	Vernot et al. 1977 para	

d = day(s); hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

No studies were located regarding gastrointestinal effects in animals following dermal exposure to cresols.

Hematological Effects. Hematological effects in a man apparently exposed to cresol dermally while working with an antiseptic solution containing concentrated mixed cresols, included methemoglobinemia with massive hemolysis and the presence of numerous large Heinz bodies in the blood (Larcan et al. 1974). Similar effects have been reported following oral exposure to cresols (see Section 3.2.2.2).

No studies were located regarding hematological effects in animals following dermal exposure to cresols.

Hepatic Effects. Necropsy revealed extensive centrilobular to mid-zonal liver necrosis in a 1-year-old baby who had 20 mL of a cresol derivative spilled on his head (Green 1975).

No studies were located regarding hepatic effects in animals following dermal exposure to cresols.

Renal Effects. A 1-year-old baby who died after a cresol derivative was spilled on his head had congested and swollen kidneys that were damaged by tubular necrosis (Green 1975). A man who fell into a vat containing a cresylic acid derivative developed anuria after 36 hours and experienced a steady increase in blood urea levels for 10 days until he died (Cason 1959). Anuria was also seen in a man who apparently absorbed cresol through the skin while working with an antiseptic solution containing concentrated mixed cresols (Larcan et al. 1974). Acute polyuric renal failure was described in a man who accidentally spilled with *m*-cresol onto both legs and face (Evers et al. 1994).

No studies were located regarding renal effects in animals following dermal exposure to cresols.

Dermal Effects. Corrosive damage to the skin has been reported in humans dermally exposed to cresols (Cason 1959; Green 1975; Herwick and Treweek 1933; Klinger and Norton 1945; Pegg and Campbell 1985). In one patient, disfiguring scars remained visible 1 year after exposure (Herwick and Treweek 1933). However, no reaction to cresol was noted when it was applied to the skin as a 1% solution in alcohol (Reimann 1933).

Cresols are also strong skin irritants in animals. All three cresol isomers, either alone or in combination, are severely irritating to rabbit skin, producing visible and irreversible tissue destruction (Vernot et al.

1977). Some cresylic acids produced induration and discoloration of the skin in rats (Campbell 1941). All reliable LOAEL values for acute dermal effects in rabbits are recorded in Table 3-2.

In a study of intermediate duration, dermal application of 0.5% *p*-cresol for 6 weeks produced permanent depigmentation of the skin and hair of mice (Shelley 1974). A caustic effect on the skin was noted in one strain of mouse, but not another. Neither *o*- nor *m*-cresol produced any color change in the mice. The investigator suggested that only *p*-cresol was active because it mimics the structure of tyrosine, the amino acid present in melanin, so that tyrosinase acts on it, liberating free radicals that damage melanocytes. NOAEL and LOAEL values were not derived from this study because the applied dose was not reported.

3.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals following dermal exposure to cresols.

3.2.3.4 Neurological Effects

Neurological effects were seen in two people who were accidentally exposed to mixed cresols on the skin and later died. A 1-year-old baby who had 20 mL of a cresol derivative spilled on his head was unconscious within 5 minutes; autopsy revealed swelling and congestion of the brain (Green 1975). A man who fell into a vat containing a cresylic acid derivative and received burns on 15% of his body fell into a coma 9 days later (Cason 1959). A man who survived a 5–6-hour immersion of his hands in a concentrated cresylic acid solution experienced persistent eye watering, followed by pain on the side of his face and, ultimately, marked facial paralysis (Klinger and Norton 1945).

Only one study reported neurological effects in animals following dermal exposure to cresols. Rapid, shallow breathing and convulsions were observed in rats 5–30 minutes after covered dermal application of 1.0–3.5 mL/kg of certain cresylic acid formulations (Campbell 1941). Other formulations had no effect. These convulsions stopped after a few hours in the rats that survived.

No studies were located regarding the following health effects in humans or animals after dermal exposure to cresols:

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

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

Cresols have not been evaluated for ability to induce cancer when applied to the skin of animals. However, a study of skin tumor promotion by cresols was located (Boutwell and Bosch 1959). Mice were given a single dermal application of 9,10-dimethyl-1,2-benzanthracene (DMBA), a cancer initiator, followed by application of 20% solutions of *o*-, *p*-, or *m*-cresol in benzene twice a week for 12 weeks. This level of cresols exposure proved to be acutely toxic, producing relatively high nontumor-related mortality. Consequently, all tumor results were based on number of survivors (14–20 per group). Promotion with cresols led to increases in the average number of skin papillomas per mouse and the percentage of exposed mice with at least one papilloma. *o*-Cresol was the most potent isomer, and *p*-cresol the least. Carcinomas were not observed following cresols exposure, although the observed papillomas have the potential to develop into carcinomas. A problem with the study was use of benzene, a known carcinogen, as the solvent for the cresols. However, benzene controls in the cresols experiment did not develop papillomas, and neither did benzene controls in four parallel series of experiments (a few papillomas were observed in a fifth benzene control group). Therefore, the results of this study showing that all three cresol isomers are capable of promoting skin tumors initiated by DMBA appear to be valid.

3.3 GENOTOXICITY

The genotoxic effects of cresols have been well studied. *In vitro* genotoxicity assays on *o*-, *p*-, and *m*-cresol are shown in Table 3-3. Results were uniformly negative in *Salmonella* assays with or without metabolic activation (Douglas et al. 1980; Florin et al. 1980; Haworth et al. 1983; Kubo et al. 2002; NTP 1992b; Pepper, Hamilton & Scheetz 1981; Pool and Lin 1982) and mixed in *in vitro* studies using mammalian cells (Brusick 1988a, 1988b, 1988c; Cifone 1988a, 1988b, Gaikwad and Bodell 2001; Hamaguchi and Tsutsui 2000; Hikiba et al. 2005; Li et al. 2005; Miyachi and Tsutsui 2005; Murli 1988, Pepper, Hamilton & Scheetz 1980, 1981). Positive results were reported in assays for chromosomal

Table 3-3. Genotoxicity of Cresols *In Vitro*

Species (test system)	End point	Results		References	Isomer
		With activation	Without activation		
Prokaryotic organisms:					
Salmonella typhimurium on plates	Reverse mutation	–	–	Douglas et al. 1980; Florin et al. 1980; Haworth et al. 1983; Kubo et al. 2002; Pepper, Hamilton & Scheetz 1980, 1981; Pool and Lin 1982	*o, p, m,* 1:1:1 mixture of *o, p, m*
Eukaryotic organisms:					
Mammalian cells:					
CHO cells	Chromosomal aberrations	+	+	Murli 1988	*o, p*
CHO cells	Chromosomal aberrations	–	–	Murli 1988	*m*
CHO cells	Sister chromatid exchange	+	+	Pepper, Hamilton & Scheetz 1980, 1981	*o*, 1:1:1 mixture of *o, p, m*
Mouse BALB/C-313 cells	Cell transformation	+	No data	Pepper, Hamilton & Scheetz 1980	1:1:1 mixture of *o, p, m*
Mouse BALB/C-313 cells	Cell transformation	No data	+	Brusick 1988b	*p*
Mouse BALB/C-313 cells	Cell transformation	–	–	Brusick 1988a, 1988b, Pepper , Hamilton & Scheetz 1981; Sernav 1989b	*o, m*
L5178Y mouse lymphoma cells	Forward mutation	+	(+)	Pepper, Hamilton & Scheetz 1980	1:1:1 mixture of *o, p, m*
L5178Y mouse lymphoma cells	Forward mutation	–	–	Cifone 1988a; Pepper, Hamilton & Scheetz 1981	*o, p, m*
Mouse spermatid	DNA damage	No data	+	Li et al. 2005	*o*
Primary rat hepatocytes	Unscheduled DNA synthesis	No data	–	Pepper, Hamilton & Scheetz 1981	*o*
Rat hepatocytes	DNA adduct formation	–	+	Gaikwad and Bodell 2001	*p*
Freshly cultured rat hepatocytes	Unscheduled DNA synthesis	No data	–	Cifone 1988b	*m*
Human peripheral lymphocytes	Semiconservative/ repair DNA	No data	(+)	Daugherty and Franks 1986	*p*
Human peripheral lymphocytes	DNA damage	No data	+	Li et al. 2005	*o*
HL-60 cells	DNA adduct formation	–	+	Gaikwad and Bodell 2001	*p*

Table 3-3. Genotoxicity of Cresols *In Vitro*

Species (test system)	End point	Results		References	Isomer
		With activation	Without activation		
Syrian hamster kidney cells	SV40 induction	No data	(+)	Moore and Coohill 1983	*m*
SHE cells	Chromosomal aberrations	+	+	Hikiba et al. 2005	*m*
SHE cells	Unscheduled DNA synthesis	+	–	Hamaguchi and Tsutsui 2000	*m*
SHE cells	Sister chromatid exchange	No data	+	Miyachi and Tsutsui 2005	*m*
Cultured human fibroblasts	Sister chromatid exchange	No data	–	Cheng and Kligerman 1984	*o, p, m*

– = negative result; + = positive result; (+) = weakly positive; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; SHE = Syrian hamster embryo

aberrations for *o*- and *p*- cresol, but not for *m*-cresol in Chinese hamster cells (Murli 1988), while *m*-cresol produced positive results for chromosomal aberrations in Syrian hamster embryo cells (Hikiba et al. 2005). There was a positive result for sister chromatid exchange for *o*-cresol and for a mixture of *o*-, *p*-, and *m*-cresol in Chinese hamster ovary cells (Pepper, Hamilton & Scheetz 1980, 1981), and Syrian hamster embryo cells (Miyachi and Tsutsui 2005), which is in contrast to negative results for sister chromatid exchange in human fibroblasts for the *o*-, *p*-, and *m*-isomers (Cheng and Kligerman 1984). *p*-Cresol, and a mixture of the *o*-, *p*-, and *m*-cresol, also produced cell transformation in mouse BALB/C-3T3 cells (Brusick 1988b; Pepper, Hamilton & Scheetz 1980), while *o*- and *m*-cresol did not (Brusick 1988a, 1988b; Pepper, Hamilton & Scheetz 1981; Sernav 1989b).

A 1:1:1 mixture of the three cresol isomers was positive in tests for forward mutation in mouse lymphoma cells (Pepper, Hamilton & Scheetz 1980), but negative for each isomer tested individually (Cifone 1988a; Pepper, Hamilton & Scheetz 1981). Assays were negative for increased DNA synthesis in rat hepatocytes for *o*- and *m*-cresols (Cifone 1988b; Pepper, Hamilton & Scheetz 1981), and positive in Syrian hamster embryo cells with activation for *m*-cresol (Hamaguchi and Tsutsui 2000) and in human peripheral lymphocytes for *p*-cresol (Daugherty and Franks 1986). DNA damage was found in mouse spermatid and human peripheral lymphocytes in assays testing *o*-cresol (Li et al. 2005), as was DNA adduct formation in rat hepatocytes and HL-60 cells incubated with *p*-cresol (Gaikwad and Bodell 2001). A weak positive result was reported for SV40 induction in Syrian hamster kidney cells (Moore and Coohill 1983). Positive results obtained in some human and animal *in vitro* tests suggest that cresols have some ability to react with DNA, and may be clastogenic under certain circumstances.

Results from *in vivo* genotoxicity assays on *o*-, *p*-, and *m*-cresol are shown in Table 3-4. Studies of the genotoxicity of cresols in animals *in vivo* reported negative results for dominant lethal, chromosomal aberrations and mouse bone marrow, alveolar macrophages, and regenerating liver cells *in vivo* (Cheng and Kligerman 1984; Ivett 1989a, 1989b, 1989c; Sernav 1989a, 1989b). Treatment of male and female $B6C3F_1$ mice with up to 2,723 or 3,205 mg/kg/day *o*-cresol, respectively, for 13 weeks did not increase the incidence of micronuclei in peripheral blood erythrocytes (NTP 1992b). Similar negative results were reported in male and female mice dosed with up to 1,513 or 1,693 mg/kg/day *m/p*-cresol, respectively (NTP 1992b). However, micronucleus frequency was increased in bone marrow from male mice injected twice intraperitoneally with 20, 40, or 80 mg/kg *o*-cresol (Li et al. 2005). Although *o*-, *p*-, and *m*-cresol and a 1:1:1 mixture of the three cresol isomers gave some indication of genotoxic activity in *in vitro* assays with mammalian cells, most *in vivo* assays were negative, with one exception. Overall, cresols do not seem to pose a genotoxic threat to humans under normal environmental exposure conditions.

Table 3-4. Genotoxicity of Cresols *In Vivo*

Species (test system)	End point	Results: With activation	Results: Without activation	References	Isomer
Eukaryotic organisms (*in vivo*):					
Mouse	Dominant lethal	No data	–	Ivett 1989a, 1989b	*o, p*
Mouse	Chromosomal aberrations (bone marrow)	No data	–	Ivett 1989b	*m*
Mouse	Sister chromatid exchange (bone marrow, alveolar macrophages, and regenerating liver cells)	No data	–	Cheng and Kligerman 1984	*o, p, m*
Mouse	Micronucleus frequency	No data	+	Li et al. 2005	*o*
Mouse	Micronucleus frequency	No data	–	NTP 1992b	*o, m/p*
Drosophila melanogaster	Sex-linked recessive lethal	No data	–	Sernav 1989a, 1989b	*o, p*

– = negative result; + = positive result

3.4 TOXICOKINETICS

Cresols can be absorbed following inhalation, oral, and dermal exposure by humans and animals. Most of the evidence of absorption in humans is indirect, derived from cases of accidental dermal contact with these substances or accidental or intentional ingestion. Limited data from workers exposed to airborne cresols provide evidence of absorption by inhalation, although dermal absorption could have also occurred. Quantitative data are not available. Little is known about distribution of cresols in humans. In a fatal case of dermal intoxication, cresols were found in the brain and liver. Studies in animals dosed by oral gavage with a single dose of *m*- or *p*-cresol indicate that cresols can distribute rapidly into many organs and tissues. Cresols undergo oxidative metabolism in the liver and are rapidly eliminated, mostly in the urine, as sulfate or glucuronide conjugates. A study showed that human and rat liver microsomes *in vitro* metabolized *p*-cresol in a similar manner. However, the relevance of the available toxicokinetics information in animals to toxicokinetics of cresols in humans is unknown.

3.4.1 Absorption

p-Cresol is normally found in the body where it is generated from protein breakdown. *p*-Cresol is one of the metabolites of the amino acid tyrosine and of phenylalanine. Tyrosine and phenylalanine are converted to 4-hydroxyphenylacetic acid by intestinal bacteria. 4-Hydroxyphenylacetic acid is further decarboxylated to *p*-cresol, which is absorbed from the intestine and excreted in the urine as conjugates (De Smet et al. 1997; Vanholder et al. 1999). De Smet et al. (1998a) reported a mean concentration of 8.6 µmol/L of *p*-cresol (0.93 mg/L) in serum from healthy subjects.

3.4.1.1 Inhalation Exposure

No studies were located regarding the rate and extent of absorption in humans following inhalation exposure to cresols.

The absorption of cresols following inhalation exposure in animals has not been quantified, but can be assumed to occur, since mortality and other effects have been reported in animals following exposure (Campbell 1941; Kurlyandskiy et al. 1975; Uzhdavini et al. 1972).

3.4.1.2 Oral Exposure

No studies were located regarding the rate and extent of absorption in humans following oral exposure to cresols. However, it can be assumed that cresol are absorbed orally based on the many reports of adverse effects in subjects who ingested cresols accidentally or intentionally (i.e., Chan et al. 1971; Hashimoto et al. 1998; Kamijo et al. 2003; Labram and Gervais 1968).

In a study in rabbits administered all three cresol isomers by oral gavage under fasting conditions, from 65 to 84% of the administered dose was recovered in the urine within 24 hours, indicating that at least that amount had been absorbed (Bray et al. 1950). When *p*-cresol was administered 1–2 hours after the rabbits were fed, the rabbits exhibited less toxic effects than when given the compound under fasting conditions, indicating that the gastrointestinal contents retarded the absorption of *p*-cresol (Bray et al. 1950). A recent study showed that after a single gavage dose of a cresol soap solution (*p*- and *m*-cresol) to rats, 50% of the administered dose disappeared from the gastric contents in 15 minutes, and almost all of the administered cresol disappeared within 8 hours (Morinaga et al. 2004). In blood, the unconjugated concentrations of *p*- and *m*-cresol decreased rapidly for 2 hours after peaking 30 minutes after dosing. No unconjugated cresols could be detected after 4 hours. The *p*-cresol glucuronide in blood was always higher than the *p*-cresol sulfate, whereas the concentration of *m*-cresol sulfate was consistently higher than the *m*-cresol glucuronide. Based on the fact that the concentrations of the unconjugated cresols in liver and spleen were much higher than those in blood over a monitoring period of 8 hours, Morinaga et al. (2004) suggested that cresol administered by oral gavage diffuses directly through the gastric and small intestinal walls.

3.4.1.3 Dermal Exposure

The occurrence of coma, death, and systemic effects in two humans dermally exposed to cresols (Cason 1959; Green 1975) indicates that these compounds can be absorbed through the skin. In another case of accidental dermal exposure to cresols, Fuke et al. (1998) reported that the concentrations of unconjugated *p*-cresol, sulfate, and glucuronide in the serum collected 2 hours after exposure were 15.7, 21.3, and 38.6 µg/mL, respectively. The respective concentrations of *m*-cresol were 31.4, 17.0, and 82.9 µg/mL; the exposure amount was unknown so that the extent of absorption could not be estimated. An *in vitro* study of the permeability of human skin to cresols found that these substances had permeability coefficients greater than that for phenol, which is known to be readily absorbed across the skin in humans (Roberts et al. 1977).

No studies were located regarding the rate and extent of absorption in animals following dermal exposure to cresols.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located regarding the extent of distribution in humans or animals following inhalation exposure to cresols.

3.4.2.2 Oral Exposure

No studies were located regarding the distribution of cresols in humans following oral exposure.

The distribution of *m*- and *p*-cresol has been studied in rats (Morinaga et al. 2004). Rats received a single gavage dose of a mixture of *m*- and *p*-cresol soap solution (100 mg *p*-cresol, 160 mg *m*-cresol/kg) and conjugated and unconjugated cresols were determined in tissues at various times up to 8 hours after dosing. The concentrations of unconjugated *m*- and *p*-cresol in liver and spleen were always much higher than in blood and higher than the sulfate or glucuronide metabolites in those organs. The unconjugated concentrations of both cresols in brain, lung, and muscle were similar to those in blood. The concentration of glucuronidated cresols were always highest in the kidney followed by the liver. Comparison of the concentration of glucuronide and sulfate conjugates in tissues showed that the glucuronide was always higher than the sulfate for both *p*- and *m*-cresol, particularly in the liver and kidneys. In all tissues, *m*-cresol sulfate was always higher than *p*-cresol sulfate, suggesting a slightly different metabolic disposition for these two isomers.

3.4.2.3 Dermal Exposure

Cresols were identified in the blood (12 mg/100 mL), liver, and brain of a 1-year-old baby who died 4 hours after 20 mL of a cresol derivative was spilled on his head (Green 1975).

No studies were located regarding the extent of distribution in animals following dermal exposure to cresols.

3.4.2.4 Other Routes of Exposure

In rats administered a single intravenous dose of 3 mg/kg of *p*-cresol, the concentration of *p*-cresol in blood 5 minutes after dosing was 6.7 mg/L and decreased gradually to 0.6 mg/L near 240 minutes after dosing (Lesaffer et al. 2001). The half-life of *p*-cresol in serum was 1.5 hours (twice as long as creatinine) and its total clearance was 23.2 mL/minute/kg (3 times that of creatinine). Also, the volume of distribution of *p*-cresol was 5 times that of creatinine; however, renal clearance of *p*-cresol (4.8 mL/minute/kg) was about half that of creatinine. Similar results were reported in a subsequent paper from the same group of investigators (Lesaffer et al. 2003a).

3.4.3 Metabolism

No studies were located regarding metabolism in humans following exposure to cresols.

A few studies reported on the metabolism of cresols in animals. Cresols in the urine are found primarily as sulfate and glucuronide conjugates. In the urine of rabbits, 60–72% of the orally administered dose was recovered as ether glucuronide, and 10–15% was recovered as ethereal sulfate (Bray et al. 1950). A similar result was obtained in an earlier study in rabbits in which 14.5–23.5% of the orally administered dose was found conjugated with sulfate in the urine (Williams 1938). For simple phenols such as cresols, the proportions of the conjugates are known to vary with dose and to differ from one species to the next. In the study by Bray et al. (1950), hydroxylation of a small percentage (3%) of the administered dose to 2,5-dihydroxytoluene (conjugated) occurred for both *o*- and *m*-cresol. No hydroxylation occurred for *p*-cresol, but *p*-hydroxybenzoic acid (both free and conjugated) was detected in the urine. Only 1–2% of the administered dose was found as unconjugated free cresol in the urine. A study in rats showed that *m*-cresol is preferentially metabolized to sulfate, and *p*-cresol to glucuronide (Morinaga et al. 2004).

Studies by Thompson and coworkers (Thompson et al. 1994, 1995, 1996) and Yan et al. (2005) have provided more detailed information on the metabolism of cresols and the role of metabolism in hepatotoxicity (the role of metabolism on hepatotoxicity is discussed in Section 3.5.2). Using rat liver microsomes and precision-cut liver slices, Thompson et al. (1995) demonstrated that *p*-cresol formed monoglutathione conjugates with a structure consistent with the formation of a quinone methide intermediate. The latter may be formed in two successive one electron oxidation steps by cytochrome P-450 (Koymans et al. 1993). Using human liver microsomes Yan et al. (2005) confirmed that the activation of *p*-cresol by oxidation forms a reactive quinone methide which formed a conjugate,

glutationyl-4-methyphenol. In addition, a new pathway was identified consisting of aromatic oxidation leading to the formation of 4-methyl-o-hydroquinone which is further oxidized to 4-methyl[1,2]benzo-quinone. The latter formed three adducts with glutathione, but the predominant was found to be 3-(glutathione-S-yl)-5-methyl o-hydroquinone. It was also found that 4-hydroxybenzylalcohol, a major metabolite formed by oxidation of the methyl group in liver microsomes, was further converted to 4-hydroxybenzaldehyde. Experiments with recombinant P-450s demonstrated that the formation of the quinone methide intermediate was mediated by several P-450s including CYP2D6, 2C19, 1A2, 1A1, and 2E1. The ring oxidation pathway was found to be mediated primarily by the CYP2E1 and to a lesser extent by CYP1A1, 1A2, and 2D6. Formation of 4-hydroxybenzaldehyde was catalyzed by 1A2 and also 1A1 and 2D6. Human liver microsomes formed the same adducts as rat liver microsomes suggesting that the metabolism of *p*-cresol is similar in humans and rats. The metabolic pathway for *p*-cresol proposed by Yan et al. (2005) is shown in Figure-3-2.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Studies of subjects occupationally exposed to cresols have demonstrated that cresols are eliminated in the urine. Workers employed in the distillation of the high temperature phenolic fraction of tar excreted *p*-and *o*-cresol in the urine at rates of 2.4 and 3.3 mg/hour, respectively (Bieniek 1994). The highest concentrations in urine were found during the first 2 hours after the end of the work shift. A study of 76 men working at a coke plant where the geometric mean concentrations of *o*-, *m*-, and *p*-cresol in the breathing zone air were 0.09, 0.13, and 0.13 mg/m^3, respectively, reported that the corresponding concentrations in hydrolyzed urine were 16.74, 16.74, and 0.53 mg/g creatinine (Bieniek 1997).

3.4.4.2 Oral Exposure

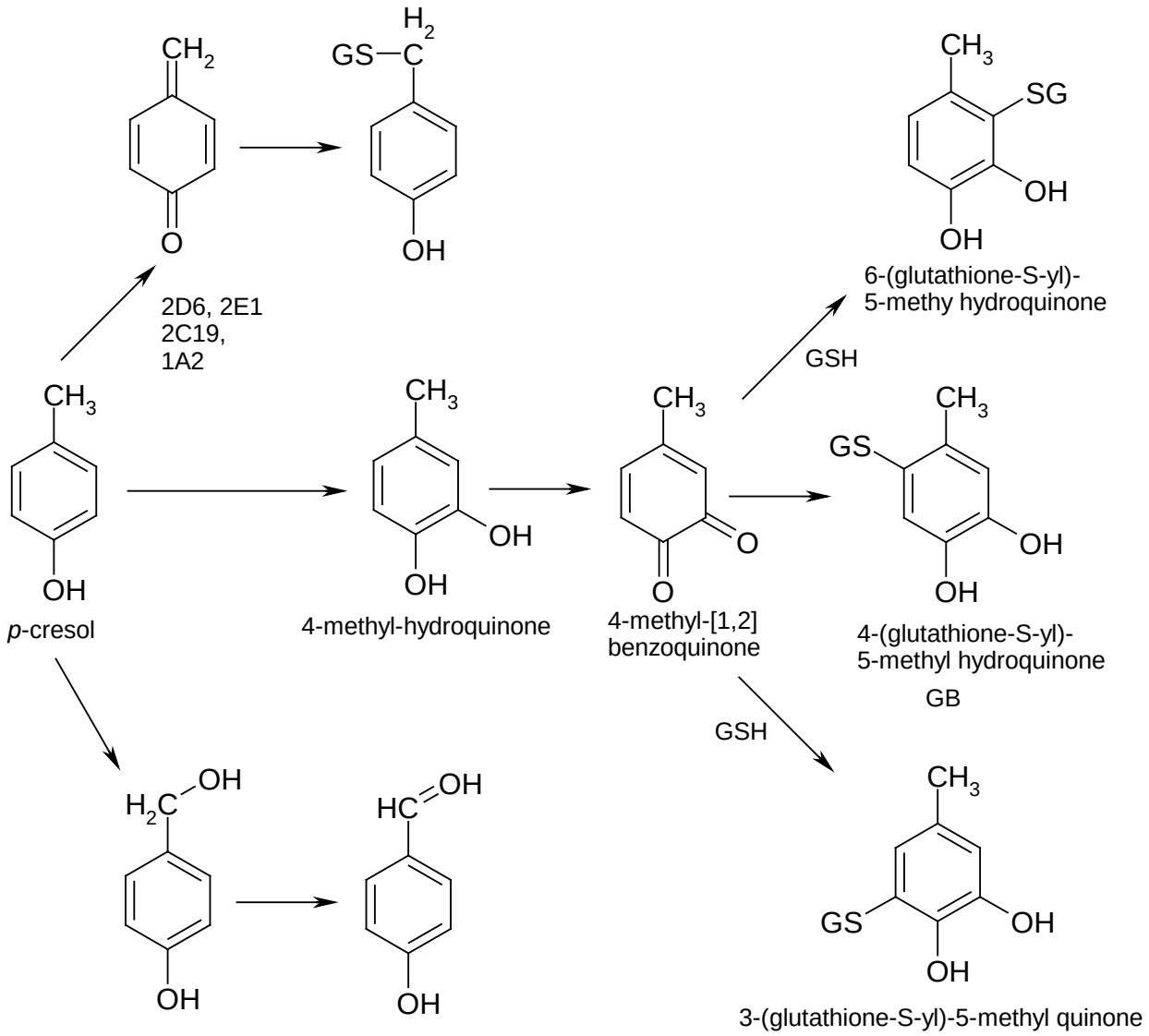
No studies were located regarding excretion in humans following oral exposure to cresols.

Following oral exposure to cresols in rabbits, 65–84% of the dose was excreted in the urine within 24 hours, mostly as ethereal glucuronides and sulfates (Bray et al. 1950).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals following dermal exposure to cresols.

Figure 3-2. Bioactivation Pathways of *p*-Cresol in Human Liver Microsomes



Source: adapted from Yan et al. 2005

3.4.4.4 Other Routes of Exposure

Intravenous injection of a single dose of *p*-cresol to rats resulted in approximately 23% of the injected dose being excreted in the urine as parent compound within 240 minutes, the duration of the experiment (Lesaffer et al. 2001). As indicated in Section 3.4.2.4, the total clearance of *p*-cresol largely exceeded its renal clearance, which led Lesaffer et al. (2001) to suggest the presence of extra-renal elimination routes for *p*-cresol, namely, exsorption from the blood compartment into the gastrointestinal tract, biotransformation, or excretion via the bile. A subsequent study from the same group of investigators showed that in rats, 64% of an intravenous dose of *p*-cresol (9.6 mg/kg) was excreted as *p*-cresylglucuronide (Lesaffer et al. 2003b). When the glucuronide and the unconjugated *p*-cresol were combined, approximately 85% of the injected dose was recovered in the urine.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

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

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

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

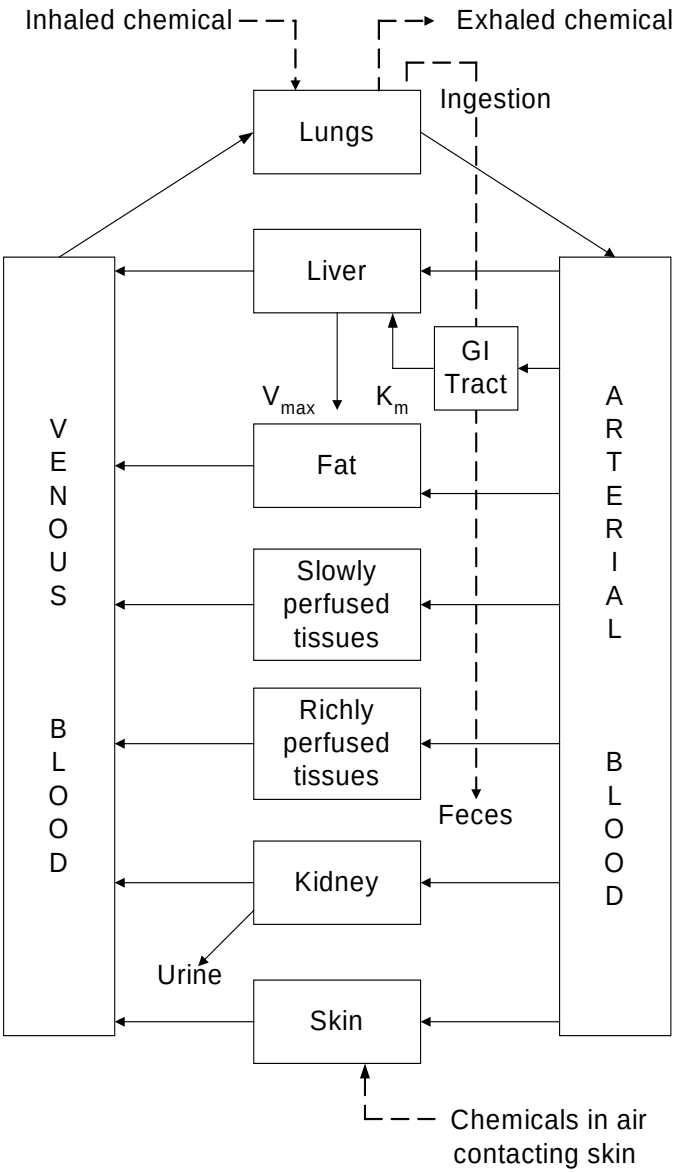
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many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

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

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

No PBPK models have been developed for cresols.

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



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

Source: adapted from Krishnan et al. 1994

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. No specific information was located regarding the mechanism of absorption of cresols. However, in a study in rats administered a cresol soap solution (*m*- and *p*-cresol) via a gastric tube, the concentration of free cresols in liver and spleen were much higher than those in blood at all times after dosing (up to 8 hours) (Morinaga et al. 2004). This led the investigators to suggest that cresol administered via a stomach tube diffuses directly though the gastric and small intestinal walls, which according to Morinaga et al. (2004), would explain the very high concentration of unconjugated cresols found in the liver and also in the spleen, which is adjacent to the stomach. Whether this also happens following ingestion of cresols mixed in food or in water is not known.

Distribution. No specific information was located regarding how cresols are transported in blood, but it is reasonable to assume that they may be bound to albumin, the most important binding protein for many acidic and basic drugs (Mabuchi and Nakahashi 1988). In a study of healthy subjects and patients with chronic renal failure, no free *p*-cresol could be detected in the blood of healthy subjects, 100% was protein-bound (De Smet et al. 1998a). No information was located for *o*- or *m*-cresol.

Metabolism. The limited information available summarized in Section 3.4.3 indicates that cresols undergo conjugation with sulfate and glucuronic acid and also form oxidative metabolites. However, there is virtually no information on possible shifts between these reactions that could be dose-dependent, dependent on the availability of co-substrates in the conjugation reactions, or related to different enzyme activity levels across areas of the liver, as occurs with structurally similar chemicals (i.e., phenol). The role of metabolism on the toxicity of cresols is discussed in Section 3.5.2.

Excretion. Cresols are excreted in the urine as glucuronides and sulfates. However, based on the observation that the total clearance of *p*-cresol largely exceeded its renal clearance in rats administered *p*-cresol intravenously, Lesaffer et al. (2001) suggested the presence of extra-renal elimination routes for *p*-cresol, namely, exsorption (reverse absorption or secretion) from the blood compartment into the gastrointestinal tract, biotransformation, or excretion via the bile. Exsorption from the blood compartment into the gastrointestinal tract may be plausible for unbound *p*-cresol, a relatively small molecule, but not for protein-bound *p*-cresol, which is how 100% of *p*-cresol is normally found in the blood (De Smet et al. 1998a). No pertinent information was located for *o*- or *m*-cresol.

3.5.2 Mechanisms of Toxicity

Limited information is available regarding the mechanism(s) of toxicity of cresols. Cresols are irritant and corrosive at high concentrations as evidenced by numerous cases of accidental dermal exposure or accidental or intentional ingestion of cresols. Much like phenol, cresols impair the stratum corneum and produce coagulation necrosis by denaturating and precipitating proteins.

The role of metabolism in the toxicity of cresol has been studied by Thompson and coworkers (Thompson et al. 1994, 1995, 1996). Using lactate dehydrogenase (LDH) leakage or intracellular potassium as indices of toxicity in precision-cut rat liver slices as a test system, they showed that *p*-cresol was the most toxic of the three isomers. Similar results were obtained in liver slices from rats pretreated with phenobarbital, an inducer of cytochrome P-450; however, in this case, the toxicity of each isomer relative to control was increased compared to untreated slices. On a molar basis, *p*-cresol was 5–10 times more toxic than *o*- or *m*-cresol in the LDH leakage test. Incubation with the thiol precursor N-acetylcysteine or inhibition of cytochrome P-450 with metyrapone inhibited the toxicity of *p*-cresol, whereas depletion of glutathione increased the toxicity of *p*-cresol. These treatments had little effect on the toxicity of *o*- or *m*-cresol, suggesting a somewhat different mechanism of action, at least in the test system used. Furthermore, *p*-cresol rapidly depleted intracellular levels of glutathione, while the other isomers did it to a lesser extent. In the absence of glutathione, the major metabolite of *p*-cresol was *p*-hydroxybenzyl alcohol, which caused no observable toxicity to the liver slices. In the presence of glutathione, the amount of *p*-hydroxybenzyl alcohol was reduced by about 30% and the new product formed was confirmed to be a glutathione conjugate formed via the formation of a reactive quinone methide intermediate. The reactive intermediate bound covalently to protein in slices and in microsomal preparations. A metabolic pathway for *p*-cresol proposed by Yan et al. (2005) is shown in Figure 3-2.

A study by Kitagawa (2001) suggested that liver mitochondria may be a target for the liver toxicity of cresols based on results that indicated that these compounds inhibited mitochondrial respiration and induced or accelerated swelling of the mitochondria. However, it is difficult to relate the results from these studies *in vitro* to the observations of little or no alterations in the liver of animals dosed with cresols for extended periods of time (NTP 1992b).

Many studies in which the animals were dosed with cresols by oral gavage reported adverse neurological signs ranging from lethargy to tremors and convulsions (EPA 1988b, 1988c; TRL 1986; Tyl 1988a, 1988b). Dietary studies reported occasional tremors only at the highest doses administered. The

mechanism by which cresols induced these effects is unknown. Studies in rats have reported that cresols induce changes in neurotransmitter levels in the brain (Calderón-Guzmán et al. 2005) and in activities of some enzymes (DeWolf et al. 1988; Savolainen 1979). Calderón-Guzmán et al. (2005) also suggested that cresols may increase lipid peroxidation and change membrane fluidity in rat brain. Studies have also reported neurophysiological changes in animals exposed to cresols. Mattsson et al. (1989) observed excitation of somatosensory evoked potentials and changes in the EEG in rats following intravenous administration of *o*-cresol. Mohammadi et al. (2001) reported that *o*-cresol, but not *m*-cresol, activated $GABA_A$ receptors expressed in transformed human embryonic kidney cells. If such an effect were to occur in the intact animal, it may result in decreased activity and sedation since GABA normally mediates inhibitory neural activity. Whether any of these putative mechanisms of neurological effects are involved in the effects observed following oral dosing of animals, particularly by gavage, is unknown. Cresols could be acting at multiple sites including sites at the periphery.

3.5.3 Animal-to-Human Extrapolations

Cresols are irritants and corrosive in high concentrations and will produce similar effects on the skin and mucosal surfaces of humans and animals. Other than death and neurological effects, which have been reported both in humans and animals exposed to high amounts of cresols, it is difficult to predict other health outcomes in humans based on observations in animals. The metabolism of cresols seems to be similar in humans and rats based on the fact that both species excrete sulfate and glucuronide conjugation products in the urine. Furthermore, Yan et al. (2005) showed that bioactivation patterns for *p*-cresol in human and rat liver microsomes lead to the same reactive intermediates and glutathione adducts. While this and other studies (Thompson et al. 1994, 1995) served to construct a toxicity ranking for cresol isomers in hepatocytes *in vitro*, extrapolation to other toxicities would be pure speculation and inappropriate.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a

naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Based on the available information, there is no evidence that cresols are endocrine disruptors in humans and little evidence in animals. A 28-day dietary study reported mild uterine atrophy in female rats dosed with 2,310 mg/kg/day of *m*-cresol or 2,060 mg/kg/day of *p*-cresol (NTP 1992b). Comparable doses of *o*-cresol or an *m/p*-cresol mixture were without significant effect. A 13-week treatment with the ≥509 mg/kg/day *m/p*-cresol in the diet significantly lengthened the estrous cycle of rats, and doses of 1,024 and 2,050 mg/kg/day induced minimal to mild uterine atrophy (NTP 1992b). In mice, exposure to ≥1,670 mg/kg/day of *o*-cresol for 28 days also induced mild atrophy of the uterus, and 4,940 mg/kg/day of *m*-cresol induced mild to moderate atrophy of the mammary gland, uterus, and ovaries (NTP 1992b). In addition, doses of 3,205 mg/kg/day of *o*-cresol for 13 weeks lengthened the estrous cycle in female mice. In these studies, there was no biologically significant effect on males' reproductive organs or on sperm parameters. In the 2-year bioassay, doses of up to 720 and 1,040 mg/kg/day *m/p*-cresol, respectively, did not induce and significant alterations in gross or microscopic morphology of reproductive organs (NTP 2008).

Multiple-generation reproductive studies that administered cresols by oral gavage (Neeper-Bradley and Tyl 1989a, 1989b; Tyl and Neeper-Bradley 1989) or through the diet (NTP 1992a, 1992c) have provided no evidence of endocrine-mediated alterations on reproduction or development.

In standard developmental toxicity studies in rats and rabbits, cresols have induced slight fetotoxicity, but only at maternally toxic doses (Tyl 1988a, 1988b). A study that treated newborn rats with *m*-cresol by gavage from postnatal day 4 through 21 reported noticeable clinical signs (tremors, hypersensitivity) with the highest dose tested, 300 mg/kg/day, but there were no alterations in the physical development or sexual maturation of the pups (Koizumi et al. 2003).

A study in which embryos of rats were incubated *in vitro* with *p*-cresol observed increased incidence of structural abnormalities such as hind limb bud absence and tail defects, but there is no evidence that this was endocrine-mediated (Oglesby et al. 1992). Additional information from studies *in vitro* is limited. Nishihara et al. (2000) reported that *p*-cresol tested positive and *o*-cresol negative for estrogenic activity in a reporter gene expression assay using yeast cells (Nishihara et al. 2000). A substance was considered positive when its activity was more than 10% of the activity of 10^{-7} M 17β-estradiol. Neither *o*-cresol nor *p*-cresol showed androgenic activity (agonist or antagonist) in stably transfected CHO-K1 cell lines, which expressed the androgen receptor (AR) and a AR-responsive luciferase gene reporter (Araki et al. 2005; Satoh et al. 2005).

Collectively, the available evidence does not suggest that cresols represent a hazard due to properties of endocrine disrupters, although a few cases of mild atrophy of female reproductive organs and lengthening of estrous cycle in rats and mice were reported for cresols, but generally at relatively high doses.

3.7 CHILDREN'S SUSCEPTIBILITY

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

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

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

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their

alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There are no studies that specifically address the health effects of exposure to cresols in children; therefore, it is unknown whether children differ from adults in their susceptibility to health effects from cresols. Only one study was located that compared the effects of *m*-cresol administered by gavage in newborn rats and young rats (Koizumi et al. 2003). Newborn rats exhibited adverse neurological signs at approximately one third the doses that affected young rats. It is unknown whether this reflects differences in pharmacokinetics or on other aspects of *m*-cresol action. Data on the effects of cresols in adults are derived almost exclusively from cases of accidental or intentional ingestion of cresol solutions (i.e., Chan et al. 1971; Hayakawa 2002; Isaacs 1922; Jouglard et al. 1971; Kamijo et al. 2003; Minami et al. 1990; Wu et al. 1998) or accidental dermal exposure (i.e., Cason 1959; Pegg and Campbell 1985). In some of these cases, death occurred. Exposure to these amounts of cresols produced corrosion at the points of contact including the skin and gastrointestinal tract. Similar effects would be expected in children exposed to high amounts of cresols. In fact, Green (1975) reported the death of a child after a cresol mixture was spilled on his head.

There is no information regarding possible adverse developmental effects in humans exposed to cresols. Some studies in animals have reported fetotoxicity at dose levels that also produced maternal toxicity (Neeper-Bradley and Tyl 1989a, 1989b; Tyl 1988a, 1988b; Tyl and Neeper-Bradley 1989). For the most part, cresols have been negative in genotoxicity tests *in vivo*. Therefore, it is unlikely that parental exposure would result in adverse childhood development or cancer development as a result of cresol exposures to parental germ cells.

There is no information regarding pharmacokinetics of cresols in children. A study of the metabolism of *p*-cresol in human liver microsomes showed that both phase I and phase II metabolic enzymes are involved in the biotransformation of *p*-cresol and that the metabolism of *p*-cresol in humans and rats is similar (Yan et al. 2005). That study and others (Thompson et al. 1994, 1995) have provided evidence that, at least in rats, phase I enzymes increase the liver toxicity of *p*-cresol *in vitro*, whereas conjugation reactions decreased the toxicity. To the extent that some of these enzymes are developmentally regulated, the metabolism, and consequently the toxicity of cresols in immature humans may be different than in adults. However, since the causative agent of cresols toxicity is still unknown, trying to predict how immature enzymatic systems could affect the toxicity of cresols in developing humans would be pure

speculation at this time. It is not known whether cresols can cross the placenta and there are no reports on levels of cresols in maternal milk.

There are no biomarkers of exposure or effect for cresols that have been validated in children or in adults exposed as children. No relevant studies were located regarding interactions of cresols with other chemicals in children or adults.

No information was located regarding pediatric-specific methods for reducing peak absorption following exposure to cresols, reducing body burden, or interfering with the mechanism of action for toxic effects.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, 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 cresols are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of

tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by cresols are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Cresols

No biomarkers that uniquely implicate exposure to cresols have been identified in humans or animals. Cresols are formed from the commonly found amino acid tyrosine, and occur naturally in human and animal tissues, fluids, and urine. Cresols are also formed as minor metabolites of toluene, and an increased presence of *o*-cresol in the body could be due to exposure to this substance, although toluene or hippuric acid in the urine seem to be more reliable indicators of occupational exposure to toluene than *o*-cresol (De Rosa et al. 1987; Fustinoni et al. 2007). The use of cresols as a biomarker of exposure to cresol would require a considerable elevation to exceed biological background levels and potential confounding from conversion of other environmental agents. There is some evidence that the presence of *o*-cresol in urine can be used as a biomarker for phenol exposure. A study of workers at a coke plant involved in the tar-distillation process found a statistically significant correlation ($p<0.001$) between low concentrations of *o*-cresol in breathing-zone air and end-of-shift urine samples (Bieniek 1997). Urinary levels of *o*-cresol were also found to be significantly higher in the urine of workers employed in the distillation of carbolic oil than in nonexposed workers (Bieniek 1994).

p-Cresol has been found to form adducts with DNA in *in vitro* systems and it has been suggested that this property might provide a biomarker to assess occupational exposure to toluene (Gaikwad and Bodell 2001, 2003).

3.8.2 Biomarkers Used to Characterize Effects Caused by Cresols

No biomarkers of effects caused by cresols have been identified in humans or animals. Data on human exposure to cresols are derived mainly from cases of acute accidental or intentional exposure to high amounts of cresol, which usually caused external burns and corrosive necrosis of the gastrointestinal tract. Generally, these types of exposures also involved liver and kidney alterations as well as other nonspecific pathologies.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Cresols are irritant and corrosive by impairing the stratum corneum and producing coagulation necrosis by denaturating and precipitating proteins, which explains the toxic effects at the sites of contact (i.e., skin, mucosal surfaces). However, there is no information on other mechanisms of toxicity for cresols. Studies with liver cells *in vitro* suggested that metabolic activation of cresols by microsomal enzymes might produce toxic reactive intermediates (Thompson et al. 1994). It is plausible that exposure to substances that induce P-450 isozymes involved in the metabolism of cresols may increase the toxicity of cresols. Similar outcomes could occur by simultaneous exposure to cresols and substances that decrease phase II metabolic reactions. However, there is no experimental evidence to support these assumptions.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to cresols than will most persons exposed to the same level of cresols in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of cresols or compromised function of organs affected by cresols. Populations who are at greater risk due to their unusually high exposure to cresols are discussed in Section 6.7, Populations with Potentially High Exposures.

Some groups have been identified that might exhibit increased vulnerability to the effects of cresols. There is very limited evidence that individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency may have increased susceptibility to hematological effects of cresols; the increase in methemoglobin formation and decrease in glutathione levels were more pronounced in blood taken from subjects with G6PD deficiency than in blood taken from normal subjects following exposure of the blood to a disinfectant containing 50% cresols *in vitro* (Chan et al. 1971).

Patients with chronic renal failure constitute another group with increased susceptibility to *p*-cresol. In these patients, the concentration of *p*-cresol in the blood is 10 times higher than in healthy subjects due to both overgrowth of intestinal bacteria responsible for *p*-cresol production and reduced renal clearance. Free serum concentrations of *p*-cresol were shown to predict mortality in hemodialysis patients (Bammens et al. 2006). It has also been suggested that *p*-cresol decreases endothelial proliferation and wound repair in uremic patients, thus contributing to the immune defect in these patients (Dou et al. 2002, 2004). In a prospective longitudinal study, the concentrations of *p*-cresol were higher in hypoalbuminemic individuals than in those with normal albumin, and free *p*-cresol was related to hospitalization for infection (De Smet et al. 2003b).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to cresols. 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 cresols. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to cresols:

Ellenhorn MJ, ed. 1997. Ellenhorn's medical toxicology. Diagnosis and treatment of human poisoning. 2nd ed. Baltimore, MD: Williams and Wilkins.

Haddad LM, Shannon MW, Winchester JF. 1998. Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: W.B. Saunders Company.

Leikin JB, Paloucek FP. 2002. Leikin and Paloucek's poisoning and toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc.

3.11.1 Reducing Peak Absorption Following Exposure

For ingestion exposure, water or milk should be given if the patient is alert and has an intact gag reflex. Activated charcoal and a cathartic can then be administered orally or by gastric tube. Because cresol is corrosive and may cause seizures, emesis should not be induced. If the eyes have been exposed, they should be thoroughly irrigated as soon as possible with running water or saline. If the skin has been exposed, it should be flushed promptly with copious amounts of water or undiluted polyethylene glycol

followed by thorough washing with soap or mild detergent and water (Bronstein and Currance 1988; Haddad et al. 1998; HSDB 2008; Leikin and Paloucek 2002; Stutz and Janusz 1988).

3.11.2 Reducing Body Burden

Procedures that might decrease the toxicity of cresols present in the bloodstream have not been identified. Although supporting data were not located, it is possible that elimination of cresols from the blood would be enhanced by alkaline diuresis, which would increase the proportion of cresols existing in the ionized state, thereby reducing reabsorption of cresols by the kidney tubules.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

No specific procedures have been developed to interfere with the mechanism of action of cresols. Treatment of individuals intoxicated with cresols is mainly supportive. Exposed individuals with evidence of central nervous system depression or seizures should be evaluated for the presence of some other underlying disorder. Diazepam or phenobarbital may be administered to alleviate seizures. Supplemental oxygen can also be administered. If pulmonary edema occurs, conventional therapy should be given. Methylene blue may be administered for treatment of methemoglobinemia. Additional information regarding the treatment of individuals exposed to cresols may be obtained from Bronstein and Currance 1988; Haddad et al. 1998; HSDB 2008; Leikin and Paloucek 2002; and Stutz and Janusz 1988.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cresols 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 cresols.

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

that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Cresols

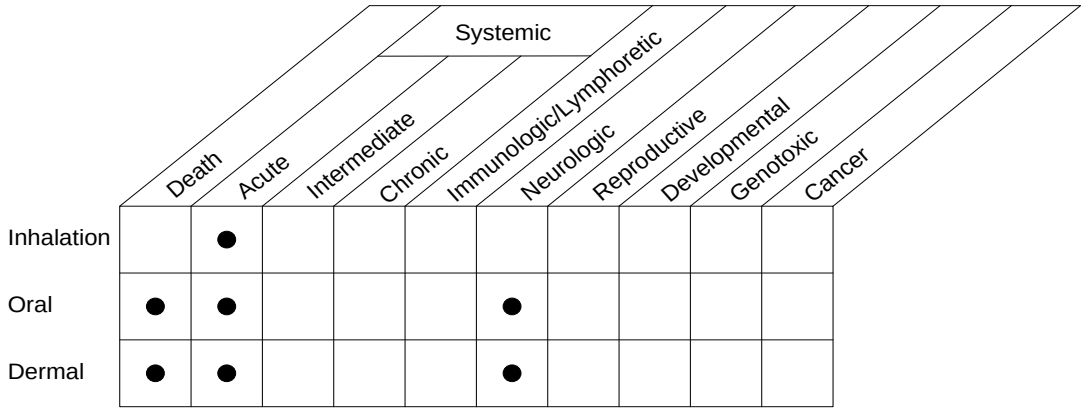
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to cresols are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of cresols. Each dot in the figure indicates that one or more 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* (Agency for Toxic Substances and Disease Registry 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.

In the following discussion, the various forms of cresol are considered together, due to the similarity of their effects and the levels at which these effects occur.

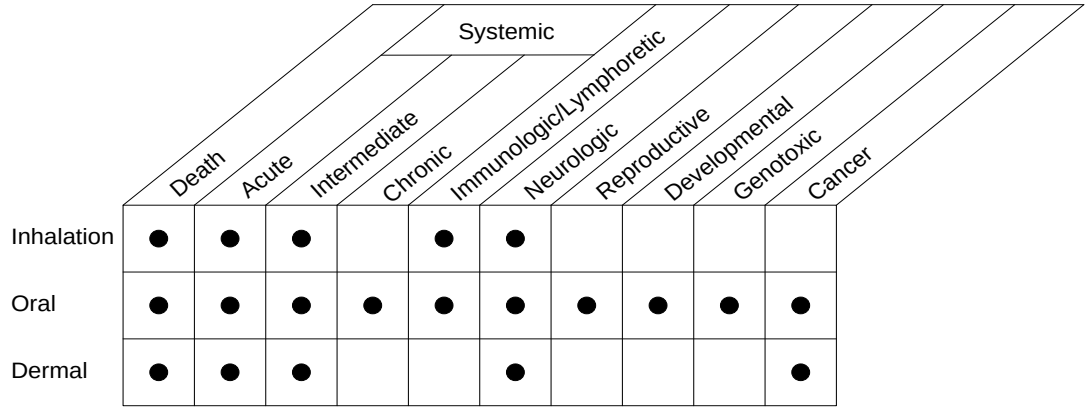
Cresols are irritants and have corrosive properties following exposure to high concentrations by any route of exposure. Therefore, the skin and mucosal membranes are targets for cresol toxicity. The existing information on the health effects of cresols in humans comes almost entirely from case reports of people who accidentally or intentionally swallowed cresol-containing substances or had these substances spilled on them. The single exception was an inhalation study of mucosal irritation in humans. Acute oral or dermal exposure to high amounts of cresol caused serious systemic effects and even death in humans.

A limited number of studies of inhalation exposure in animals tried to determine lethal levels or evaluated systemic and neurologic end points. A much greater number of studies in animals have been conducted by the oral route. Evaluation of the oral database suggests that a distinction should be made between studies by oral gavage and dietary studies based on differences on end points affected and threshold levels. Cresols are much more toxic when administered by oral gavage than when given in the diet. The difference is most likely related to differences in pharmacokinetics between the two means of administration. Animals exposed to cresols by gavage often showed adverse neurological signs and decreased weight gain associated with decreased food consumption. Oral gavage studies evaluated

Figure 3-4. Existing Information on Health Effects of Cresols



Human



Animal

● Existing Studies

reproductive, developmental, and neurological end points. Longer-term dietary studies examined systemic end points as well as reproductive, developmental, and carcinogenic effects. Studies of dermal exposure to cresols in animals generally looked at levels of lethality and irritation to the skin and eyes. One study of intermediate duration investigated dermal effects. A cancer-promotion study was also performed using dermally applied cresols.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Case reports of humans exposed to high doses of cresols, either orally or dermally, have provided acute toxicity information. Fatalities due to ingestion and dermal exposure have been described (Bruce et al. 1976; Cason 1959; Chan et al. 1971; Green 1975; Isaacs 1922; Labram and Gervais 1968; Monma-Ohtaki et al. 2002). Other effects reported in these acute high exposure scenarios include respiratory failure (Liu et al. 1999), tachycardia and ventricular fibrillation (Labram and Gervais 1968), abdominal pain, vomiting, and corrosive lesions of the gastrointestinal tract (Hayakawa 2002; Isaacs 1922; Jouglard et al. 1971; Kamijo et al. 2003; Wu et al. 1998; Yashiki et al. 1990), methemoglobinemia (Chan et al. 1971; Minami et al. 1990), leukocytosis and hemolysis (Cote et al. 1984; Wu et al. 1998), hepatocellular injury (Chan et al. 1971; Hashimoto et al. 1998; Hayakawa 2002; Kamijo et al. 2003), renal alterations (Chan et al. 1971; Isaacs 1922; Labram and Gervais 1968; Wu et al. 1998), skin damage (Cason 1959; Green 1975; Herwick and Treweek 1933; Klinger and Norton 1945; Pegg and Campbell 1985), metabolic acidosis (Hayakawa 2002; Kamijo et al. 2003), and unconsciousness (Chan et al. 1971; Isaacs 1922; Labram and Gervais 1968). Many of these effects may not have been caused directly by cresols, but represent secondary reactions to shock caused by external and internal burns. A single study in volunteers reported that brief exposures to 6 mg/m^3 of *o*-cresol in the air caused respiratory tract irritation (Uzhdavini et al. 1972).

Limited data on acute inhalation effects were available from only two studies (Campbell 1941; Uzhdavini et al. 1972) in which exposure involved mixtures of vapors and aerosols that provided insufficient information to estimate exposure levels reliably; therefore, an acute-duration inhalation MRL for cresols was not derived. Still, these studies provided some data on lethality of airborne cresols as well as information on the respiratory system (irritation), liver (fatty degeneration and necrosis), renal (tubular degeneration), and nervous system (excitation, fatigue, convulsions). Inhalation studies that use modern methodology to generate and control exposure atmospheres and that evaluate a wide range of end points may be considered in order to construct dose-response curves for acute inhalation exposure. However, under normal circumstances, acute inhalation exposure is generally not considered hazardous due to

cresols' low vapor pressure and a distinct odor at <1 ppm (NTP 1992b). A study of acute dermal exposure of animals to cresols determined exposure levels that produce skin irritation and death (Vernot et al. 1977); it is unclear what new key information would be provided by additional dermal studies. All acute-duration oral studies in animals administered cresols by oral gavage, a dosing mode that, as discussed in Section 2.3, induces different effects than those observed in dietary studies and is not considered relevant for risk assessment. Oral gavage studies showed reduced body weight, neurotoxicity, fetotoxicity, and death in exposed animals (EPA 1988b, 1988c, 1988d; TRL 1986; Tyl 1988a, 1988b). No acute dietary or drinking water studies were located for cresols, and for that reason, no acute-duration oral MRLs were derived. Although drinking water studies would mimic exposure to contaminated water at or near a waste site, the solubility of cresols would limit the high doses to be around 2%. In addition, the odor and taste of cresols may pose potential palability problems. Therefore, acute-duration dietary studies are needed for defining targets and generating dose-response relationships for this exposure duration.

Intermediate-Duration Exposure. No information is available regarding humans exposed to cresols for an extended period of time. One of the studies that provided acute-duration inhalation data also provided intermediate-duration inhalation data (Uzhdavini et al. 1972). Rodents exposed to cresols showed adverse respiratory, cardiovascular, hepatic, renal, and neurological effects, but the methods used at the time to generate and monitor the exposure atmospheres were inadequate to estimate exposure concentrations with any precision. Modern studies are needed to define targets of toxicity and to establish dose-response relationships. It would be important to determine whether the nasal lesions observed in rats and mice in the dietary study conducted by NTP (1992b) also appear in animals exposed by inhalation. If so, the intermediate-duration oral MRL for cresols (see below) may have to be revisited (this also applies for chronic-duration exposure).

Oral gavage studies of intermediate duration in animals have been performed for all three cresol isomers, and have helped to identify the levels at which cresols produce neurological, respiratory, hepatic, renal, hematological, and body weight changes in orally exposed animals (EPA 1988b, 1988c, 1988d; TRL 1986). However, gavage administration of cresols induces different effects than those observed in dietary studies and do not resemble human environmental exposure scenarios to cresols. Therefore, only dietary studies were considered for MRL derivation even though some LOAELs by gavage are lower than dietary LOAELs. NTP (1992b) tested the cresol isomers and a mixture of *m*- and *p*-cresol in 28-day and 13-week dietary studies in rats and mice. A comprehensive number of end points were examined and the critical effect was nasal lesions in both species exposed to *p*-cresol and *m/p*-cresol. The data from the 13-week

study in rats exposed to *m/p*-cresol were used to derive an intermediate-duration oral MRL for cresols. Additional intermediate oral studies do not seem necessary at this time since the NTP (1992b) study evaluated a comprehensive number of end points and cresols exhibited relatively little toxicity. Only one intermediate-duration dermal study in animals was located (Shelley 1974). People living near waste sites may be exposed to cresols in soil or dermally through water contaminated with cresols. Therefore, additional intermediate-duration dermal exposure studies are needed.

Chronic-Duration Exposure and Cancer. No studies of chronic duration were found in humans. Information regarding chronic toxicity is important because people living near hazardous waste sites might be exposed to cresols for many years. A mixture of *m/p*-cresol was tested in male Fischer-344 rats and female B6C3F_1 mice in a 2-year toxicity and carcinogenicity bioassay sponsored by NTP (NTP 2008). Although the study is yet to be finalized, preliminary results confirmed the presence of nasal lesions reported in the 28-day and 13-week studies (NTP 1992b) and also observed increased incidences of bronchiolar hyperplasia and follicular degeneration of the thyroid gland in treated mice (0, 100, 300, and 1,040 mg/kg/day). The data for bronchiole hyperplasia and follicular degeneration of the thyroid gland in female mice exposed for 2 years were used to derive a chronic-duration oral MRL for cresols. Additional long-term studies do not seem necessary at this time.

No studies were located regarding the carcinogenicity of cresols in humans. In a 2-year NTP-sponsored bioassay, an *m/p*-cresol mixture administered in the diet to male Fischer-344 rats and female B6C3F_1 mice induced a nonsignificant increase in the incidence of renal tubule adenoma in rats at 720 mg/kg/day, which was considered an equivocal finding of carcinogenicity by NTP (2008); no other neoplastic effects were reported in rats. In mice, treatment with 1,040 mg/kg/day *m/p*-cresol induced a significant increase in the incidence of squamous cell papilloma in the forestomach. Additional carcinogenicity bioassays do not seem necessary at this time.

Genotoxicity. No data were located regarding the genotoxicity of cresols in humans *in vivo*. *In vitro* studies using cultured human cells were negative for sister chromatid exchange for all three isomers (Cheng and Kligerman 1984) and positive for unscheduled DNA synthesis for *p*-cresol (Daugherty and Franks 1986). Studies of the genotoxicity of cresols in animals *in vivo* reported negative results (Cheng and Kligerman 1984; Ivett 1989a, 1989b, 1989c; NTP 1992b; Sernav 1989a, 1989b) with the exception of one study (Li et al. 2005). Results were mixed in *in vitro* studies using mammalian cells (Brusick 1988a, 1988b, 1988c; Cifone 1988a, 1988b; Murli 1988; Pepper, Hamilton & Scheetz 1980, 1981), and uniformly negative in *Salmonella* assays (Douglas et al. 1980; Florin et al. 1980; Haworth et al. 1983;

Kubo et al. 2002; NTP 1992b; Pepper, Hamilton & Scheetz 1981; Pool and Lin 1982). The positive results obtained in some human and animal *in vitro* tests suggest that cresols have some ability to react with DNA. It is unlikely that additional tests will provide new key information regarding the genotoxicity of cresols.

Reproductive Toxicity. There are no data available regarding the reproductive effects of cresols in humans. Studies in animals do not suggest that reproductive end points are sensitive targets for cresols toxicity (EPA 1988b, 1988c, 1988d; Hornshaw et al. 1986; Neeper-Bradley and Tyl 1989a, 1989b; NTP 1992a, 1992b, 1992c, 2008; Tyl and Neeper-Bradley 1989). The well-conducted dietary continuous breeding protocol studies in mice with *o*-cresol and *m/p*-cresol found no evidence of reproductive toxicity for *o*-cresol (NTP 1992a); *m/p*-cresol, at a dose that caused minor maternal toxicity, produced a decrease in the number of pups/litter and increased the cumulative days to litter, but did not affect other reproductive function end points (NTP 1992c). In the intermediate-duration dietary studies in rats and mice conducted by NTP (1992b), effects were limited to mild to moderate uterine atrophy and lengthening of the estrous cycle, generally at the highest dose levels tested. In the 2-year bioassay in male rats and female mice dosed with up to 720 and 1.040 mg *m/p*-cresol/kg/day, respectively, there were no gross or microscopic alterations in the reproductive organs (NTP 2008). There is no reason to believe that potential reproductive effects might be route-dependent. Additional studies do not seem warranted at this time.

Developmental Toxicity. There are no data available regarding the developmental effects of cresols in humans. The developmental toxicity of cresols in animals was evaluated in a series of studies in which pregnant rats and rabbits were exposed by oral gavage to each cresol isomer (Neeper-Bradley and Tyl 1989a, 1989b; Tyl 1988a, 1988b; Tyl and Neeper-Bradley 1989) and in pregnant mice exposed to *o*-cresol or *m/p*-cresol in the diet in continuous breeding protocol studies (NTP 1992a, 1992c). These studies generally reported mild fetotoxicity only at maternally toxic doses. Additional information was provided by a comparative study that observed tremors in newborn mice exposed to 100 mg/kg/day *m*-cresol on postnatal days 4–21, but none in adults exposed to up to 300 mg/kg/day for 28 days (Koizumi et al. 2003). The reason why this occurs is not known, but it is likely related to differences in the metabolic disposition of *m*-cresol between the two age groups. There is no indication that potential developmental effects of cresols could be route-dependent. Since the data from gestation exposure studies in animals indicate that developmental effects occur only at dose levels that affect the mother, further studies examining the potential developmental toxicity of cresols do not seem necessary at this time.

Immunotoxicity. No immunological effects were reported in case studies of human exposure. No significant alterations in weight or histology of lymphoreticular organs have been observed in animals following cresol exposure (EPA 1988b, 1988c, 1988d; Hornshaw et al. 1986; NTP 1992b, 2008). The information available does not suggest that the immune system is a target for cresol toxicity, but immunocompetence has not been evaluated.

Neurotoxicity. A common feature of oral poisoning with cresols in humans is coma (Chan et al. 1971; Isaacs 1922; Labram and Gervais 1968). Accidental dermal exposure of a cresol derivative was fatal to a child (Green 1975) and produced facial paralysis in a man who spilled cresol on his face (Klinger and Norton 1945). Oral gavage studies in rodents often induced adverse clinical signs indicative of neurological impairment such as hypoactivity, excessive salivation, labored respiration, and tremors (Neeper-Bradley and Tyl 1989a, 1989b; TRL 1986; Tyl and Neeper-Bradley 1989). In no cases have gross or microscopic alterations of the brain, spinal cord, or sciatic nerve been observed. None of the clinical signs seen in oral gavage studies have been seen in dietary studies (NTP 1992b, 2008), or if seen, they have occurred at much higher dose levels than in oral gavage studies. This difference is probably related to the different disposition of cresols and metabolites between the two modes of oral dosing. The mechanism(s) by which cresols induce these effects is not known, but could include actions at both central and peripheral sites of the nervous system. There is no reason to believe that the neurotoxic effects of cresols are route-dependent. Studies aimed at elucidating these mechanisms of action would be informative, but from the point of view of hazard identification, the nervous system is not a sensitive target for cresols administered at environmentally relevant levels by relevant routes of exposure.

Epidemiological and Human Dosimetry Studies. As previously mentioned, information about the effects of cresols in humans is derived mainly from case reports of accidental or intentional ingestion of cresol solutions or from accidental contact of cresol with the skin. Specific effects and references are mentioned under *Acute-Duration Exposure*. Doses were generally not available in the acute oral case reports, but Chan et al. (1971) estimated that roughly 2 g/kg may have caused the death of a woman. No group of the general population has been identified as having being exposed exclusively or predominantly to low levels of cresols for a long time. Based on data from long-term dietary studies in animals, it would be difficult to determine what specific end points to monitor in humans exposed to cresols since cresols caused relatively little systemic toxicity in the animal studies; hyperplastic or metaplastic lesions in the nasal respiratory epithelium were the most sensitive effects identified in rats and mice.

Biomarkers of Exposure and Effect.

Exposure. No biomarkers of exposure to cresols have been identified. In fact, even the cresols themselves cannot be considered specific biomarkers for cresol exposure because they are also formed as breakdown products of toluene and tyrosine. However, if toluene exposure could be ruled out, then a high level of cresols or metabolites in the blood or urine would strongly suggest cresol exposure. *p*-Cresol was found to form adducts with DNA in *in vitro* systems (Gaikwad and Bodell 2001, 2003); however, even if it does the same *in vivo*, identification of adducts would not necessarily indicate exposure to cresols for the same reasons mentioned above.

Effect. No specific biomarkers of effect have been identified for cresols. Since cresols are irritants and corrosive at high concentration, their main effects are at sites of contact (i.e., skin, respiratory, and gastrointestinal tract). Other effects observed in subjects exposed acutely to relatively high amounts of cresols (i.e., hepatic, renal, hematological, and metabolic) may be secondary to the external and internal injuries (burns) caused by cresols. It seems unlikely that specific biomarkers of effect will be identified for cresols.

Absorption, Distribution, Metabolism, and Excretion. Case reports and a limited number of studies in animals suggest that cresols are well absorbed by all routes of exposure, although quantitative data are lacking. Only one study was located that provided information on the distribution of *m*- and *p*-cresol in rats following an oral gavage dose (Morinaga et al. 2004). Cresols were found to distribute widely among tissues and no specific organ seemed to preferentially accumulate cresols. The intermediate-duration oral MRL for cresols is based on nasal effects in rats administered the test material in the diet (NTP 1992b). Since there is the possibility that the lesions may be caused by inhalation of vapors of cresol from the food, a particularly valuable study would be to administer radiolabeled cresols by gavage and determine whether cresol-derived radioactivity appears disproportionately in the nasal epithelium.

The basic metabolic reactions for cresols are known (Bray et al. 1950; Morinaga et al. 2004; Williams 1938). The metabolism of *p*-cresol has been examined in more detail in rat liver microsomes and liver slices (Thompson et al. 1994, 1995, 1996; Yan et al. 2005). These studies suggested that a reactive intermediate plays a role in the toxicity of *p*-cresol on liver cells *in vitro*, but the relevance of this finding to studies *in vivo* is unknown since cresols exhibited little or no liver toxicity in dietary studies in rats and mice (NTP 1992b).

Lacking from the cresol database are studies comparing the pharmacokinetics of cresols administered by oral gavage and in the diet. This is important because the effects of cresols administered by gavage are different than those seen following dietary administration. Based on information on a similar chemical, phenol, it is likely that the toxicity of cresols correlate with peak blood concentration rather than with total dose, but this has not been experimentally demonstrated for cresols. Information on possible dose dependency of the phase II metabolism is also lacking. It would be valuable to know for the various isomers which conjugation reaction, with sulfate or glutathione, predominates at low and high doses, and at what level each reaction might become saturated. No PBPK models have been developed for cresols. Such models are needed for addressing interspecies issues related to saturable pathways associated with various dosing parameters such as ingestion from food or water, issues related to gavage dosing, and inhalation and dermal absorption.

Comparative Toxicokinetics. The limited information available suggests that the metabolism of cresols is similar in humans and rats based on the fact that both species excrete sulfate and glutathione conjugation products in the urine. In addition, a recent study showed that bioactivation patterns for *p*-cresol in human and rat liver microsomes led to the same reactive intermediates and glutathione adducts (Yan et al. 2005). This information is insufficient to predict whether humans and animals will exhibit similar effects under similar exposure conditions, with the exception of portal-of-entry effects. However, it is unclear what practical information would provide additional comparative toxicokinetics studies given that cresols showed little systemic toxicity in animal studies when administered by an environmentally relevant route of exposure (other than nasal lesions) and no reports were found on humans exposed to cresols for long periods of time.

Methods for Reducing Toxic Effects. Cresols are strong irritants and corrosive at high concentrations and, therefore, their main effects are on surfaces with which they come in contact, such as the skin, and respiratory and gastrointestinal epithelia. Cresols exhibited little systemic toxicity in a limited number of intermediate-duration dietary studies in animals; therefore, attempts to suggest studies to counteract a yet unknown mechanism of action seem impractical at this time. The treatment for high dermal or oral exposures to cresols is standard for chemical burns and mainly supportive. Development of new therapies for the treatment of skin burns will help subjects accidentally exposure to cresols and similar chemicals.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There are no studies that specifically addressed exposure to cresols in children. Data on the effects of cresols in adults are derived almost exclusively from cases of accidental or intentional ingestion of cresol solutions (see above *Acute-Duration Exposure* for specific references). Exposure to these high amounts of cresols produced corrosion at the points of contact including the skin and gastrointestinal tract. Similar effects would be expected in children exposed to high amounts of cresols. There is no information on whether the developmental process is altered in humans exposed to cresols. Studies in animals suggest that fetotoxicity occurs only with doses of cresols that are also toxic to the mother (Neeper-Bradley and Tyl 1989a, 1989b; Tyl 1988a, 1988b; Tyl and Neeper-Bradley 1989) and further standard developmental toxicity studies do not appear necessary at this time. A study showed that newborn rats (exposed daily on postnatal days 4–21) were more sensitive to the neurological effects of bolus doses of cresols than young rats (exposed daily for 28 days) (Koizumi et al. 2003). This may be due to age-related differences in toxicokinetics.

There are no data to evaluate whether toxicokinetics of cresols in children are different from adults. There is no information on whether cresols can cross the placenta and there are no studies on whether cresols can be transferred from mother to offspring through maternal milk. Research into the development of biomarkers of exposure for cresols would be valuable for both adults and children. There are no data on the interactions of cresols with other chemicals in children. There are no pediatric-specific methods to mitigate the effects of exposure to high amounts of cresols. Based on the information available, it is reasonable to assume that the supportive methods recommended for maintaining vital functions in adults, will also be applicable to children.

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

3.12.3 Ongoing Studies

No ongoing studies pertaining to cresols were identified in the Federal Research in Progress database (FEDRIP 2008).