2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of 2,3-benzofuran and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for 2,3-benzofuran based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (less than 15 days), 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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with the carcinogenic effects of 2,3-benzofuran are indicated in Figure 2-l. Cancer effects could occur at lower exposure levels, but excess risks have not been estimated.

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

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

No studies were located regarding the following health effects in humans or animals after inhalation exposure to 2,3-benzofuran:

2.2.1.1 Death
2.2.1.2 Systemic Effects
2.2.1.3 Immunological Effects
2.2.1.4 Neurological Effects
2.2.1.5 Developmental Effects
2.2.1.6 Reproductive Effects
2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to 2,3-benzofuran. Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after inhalation exposure to 2,3-benzofuran.

2.2.2 Oral Exposure

No studies were located regarding health effects in humans after oral exposure to 2,3-benzofuran.

Most information about the health effects of 2,3-benzofuran comes from studies of animals (rats and mice) exposed by gavage, particularly a study by the National Toxicology Program (NTP 1989). Table 2-l and Figure 2-1 present a summary of studies that provide reliable quantitative data on the toxicity of 2,3-benzofuran following oral exposure. The main conclusions from these studies are discussed below.

TABLE 2-1. Levels of Significant Exposure to 2,3-Benzofuran - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(GO)	14 d 1x/d		250		500 (1/5 females died)	NTP 1989
2	Mouse	(GO)	14 d 1x/d		250			NTP 1989
Systemic								
3	Rat	(GO)	14 d 1x/d	Resp	250	500 (red nasal discharge)		NTP 1989
				Cardio	250			
				Gastro	250			
				Hemato	250			
				Musc/skel	250			
				Hepatic	250			
				Renal	250			
				Derm/oc	250	500 (red ocular discharge)		
				Other	125	250 (decreased body weight in males)		
4	Mouse	(GO)	14 d 1x/d	Resp	250			NTP 1989
				Cardio	250			
				Gastro	250			
				Hemato	250			
				Musc/skel	250			
				Hepatic	250			
				Renal	250			
				Derm/oc	250			
				Other	250			
INTERMEDIATE EXPOSURE								
Death								
5	Rat	(GO)	13 wk 5d/wk 1x/d		125		250 (1/10 females died)	NTP 1989
6	Mouse	(GO)	13 wk 5d/wk 1x/d		125		250 (1/10 males died)	NTP 1989

TABLE 2-1 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Systemic								
7	Rat	(GO)	13 wk 5d/wk 1x/d	Resp	500			NTP 1989
				Cardio	500			
				Gastro	500			
				Hemato	500			
				Musc/skel	500			
				Hepatic		125 (necrosis of hepatocytes in males)		
				Renal	125	250 (tubular nephropathy)		
				Derm/oc	500			
				Other	62.5	125 (reduced body weight in males)		
8	Mouse	(GO)	13 wk 5d/wk 1x/d	Resp	500			NTP 1989
				Cardio	500			
				Gastro	500			
				Hemato	500			
				Musc/skel	500			
				Hepatic	500			
				Renal	125	250 (tubular cell necrosis in males)		
				Derm/oc	500			
				Other	250	500 (reduced body weight in males)		
CHRONIC EXPOSURE								
Death								
9	Rat	(GO)	103 wk 5d/wk 1x/d				30 (decreased survival in males after 1.5 years)	NTP 1989
10	Mouse	(GO)	103 wk 5d/wk 1x/d				120 (decreased survival in females after 1.5 years)	NTP 1989

TABLE 2-1 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Systemic								
11	Rat	(GO)	103 wk 5d/wk 1x/d	Resp	120[b]			NTP 1989
				Cardio		30 (mineralization of pulmonary artery in males)		
				Gastro		30 (forestomach inflammation in males)		
				Hemato	120[b]			
				Musc/skel	120[b]			
				Hepatic	120[b]			
				Renal			30 (severe nephropathy in males)	
				Derm/oc	120[b]			
				Other		30 (reduced body weight in males)		
12	Mouse	(GO)	103 wk 5d/wk 1x/d	Resp		60 (lung hyperplasia in males)		NTP 1989
				Cardio	240[c]			
				Gastro	60	120 (forestomach hyperplasia in females)		
				Hemato	240[c]			
				Musc/skel	240[c]			
				Hepatic		60 (multinuclear hepatocytes in males)		
				Renal	240[c]			
				Derm/oc	240[c]			
				Other		60 (reduced body weight in males)		
Cancer								
13	Rat	(GO)	103 wk 5d/wk 1x/d				120 CEL (kidney adenocarcinoma in females)	NTP 1989

TABLE 2-1 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
14	Mouse	(GO)	103 wk 5d/wk 1x/d				60 CEL (lung, liver and forestomach tumors in males)	NTP 1989

[a]The number corresponds to entries in Figure 2-1.
[b]NOAEL for effect in female rats. NOAEL in male rats is 60 mg/kg/day.
[c]NOAEL for effect in female mice. NOAEL in male mice is 120 mg/kg/day.

Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Derm/oc = dermal/ocular; (GO) = gavage-oil; Gastro = gastrointestinal; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = time(s)

FIGURE 2-1. Levels of Significant Exposure to 2,3-Benzofuran – Oral

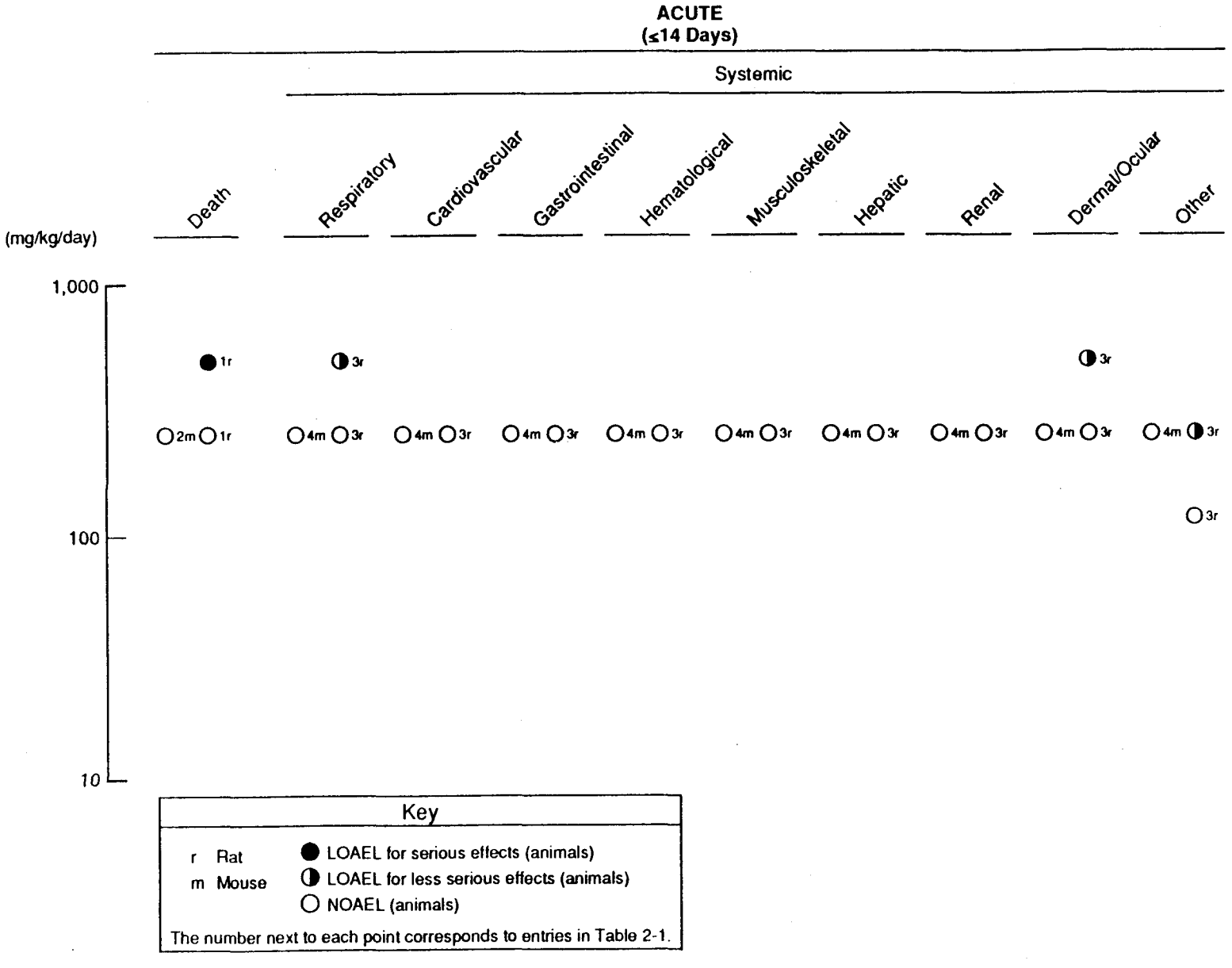


FIGURE 2-1 (Continued)

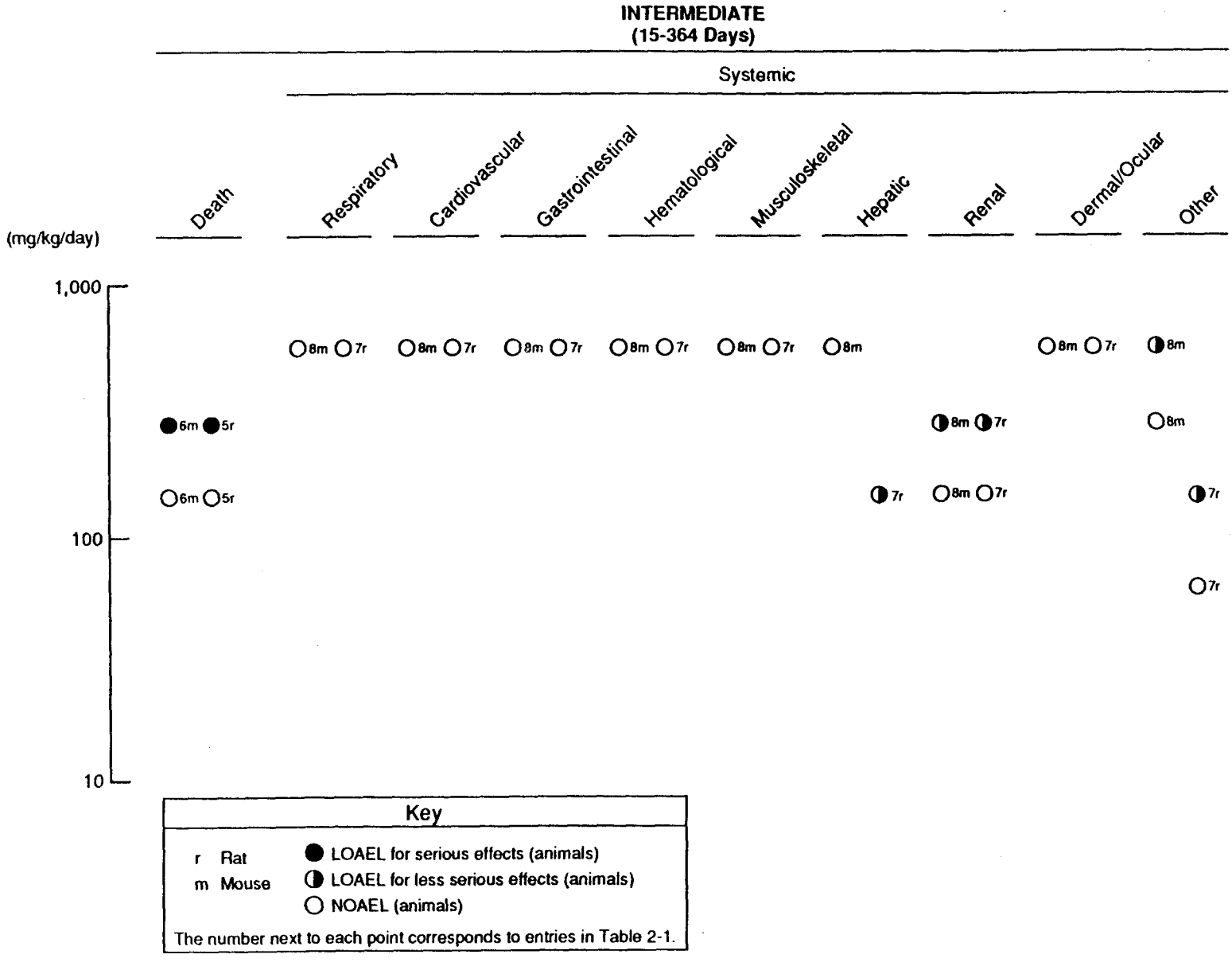
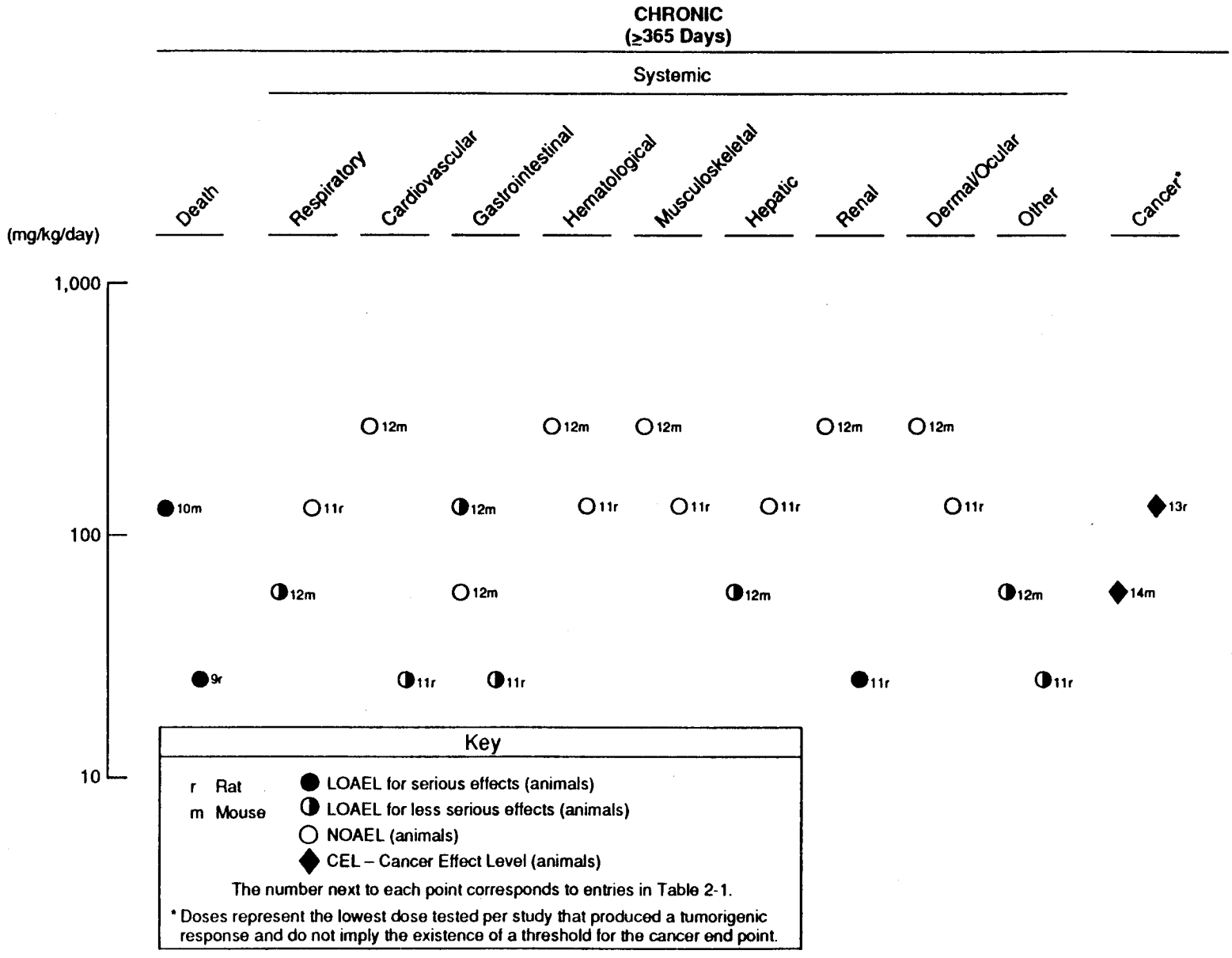


FIGURE 2-1 (Continued)



2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to 2,3-benzofuran. Oral exposure to 2,3-benzofuran can be lethal to animals. One female rat given a dose of 500 mg/kg/day died after 4 days, although 4 other female rats and all 5 male rats given this dose survived for 14 days (NTP 1989). All 10 rats given an oral dose of 1,000 mg/kg/day died within 3 days (NTP 1989). The cause of death was not determined for the rats that died following acute exposure to 2,3-benzofuran (NTP 1989). Some deaths were observed among male and female mice in groups orally exposed for 14 days to doses of 2,3-benzofuran ranging from 31.25 to 250 mg/kg/day (NTP 1989). However, all mice dying early showed evidence of gavage error (oily fluid in the pleural cavity), and the pattern of deaths showed no dose-response relationship (NTP 1989), so that no deaths among mice were attributable to chemical exposure.

Some mortality was seen among animals orally exposed to 2,3-benzofuran for 13 weeks, although the pattern of mortality was somewhat inconsistent. Among rats, 1 female out of 10 given 250 mg/kg/day died in week 1, 1 female out of 10 given 500 mg/kg/day died in week 5, and no male rats died (NTP 1989). The cause of death was not determined for the rats that died following intermediate-duration exposure to 2,3-benzofuran (NTP 1989). A NOAEL of 125 mg/kg/day and a LOAEL of 250 mg/kg/day is identified for death in rats by this study. Among mice exposed for 13 weeks, discounting deaths attributable to gavage error, 1 out of 10 males given 62.5 mg/kg/day died in week 13, no animals given 125 mg/kg/day died, 1 out of 10 males given 250 mg/kg/day died in week 12, and 4/7 males and 2/9 females given 500 mg/kg/day died in weeks 1 and 3 (NTP 1989). The cause of death was not determined for the mice that died following intermediate-duration exposure to 2,3-benzofuran (NTP 1989). The dose response relationship in this study was inconsistent, but the weight of evidence is compatible with a NOAEL of 125 mg/kg/day and a LOAEL of 250 mg/kg/day for death in mice.

Chronic exposure of male rats to 2,3-benzofuran caused a statistically-significant decrease in survival at doses of 30 and 60 mg/kg/day, attributed to increased severity of kidney damage (NTP 1989). The survival of female rats exposed to 60 and 120 mg/kg/day for 103 weeks was not significantly different from controls (NTP 1989). Female mice exposed to 120 and 240 mg/kg/day had a statistically-significant reduction in survival after 96 weeks, while the survival of male mice exposed to 60 and 120 mg/kg/day for 103 weeks was not different from controls (NTP 1989). When the dose of 2,3-benzofuran was inadvertently increased from 60 to 240 mg/kg/day for male mice in weeks 20-21, 10 out of 50 animals died (NTP 1989). No cause of death was reported for those male mice nor was a cause of decreased survival reported for female mice (NTP 1989). No NOAEL for mortality following chronic-duration exposure to 2,3-benzofuran is identified by this study.

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

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or dermal/ocular effects in humans after oral exposure to 2,3-benzofuran.

The systemic effects observed in animals after oral exposure to 2,3-benzofuran are discussed below. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-1.

Respiratory Effects. Rats exposed to oral doses of 500 and 1,000 mg/kg/day of 2,3-benzofuran for up to 14 days exhibited a red nasal discharge, which was not further characterized (NTP 1989). Histological examinations were performed only on animals in the 250 mg/kg/day dose groups (NTP 1989). Histological examination of nasal, larynx, trachea, lung, and bronchial tissues of rats and mice exposed to 2,3-benzofuran by gavage for up to 2 years showed compound-related hyperplasia in the lungs and nasal mucosa in chronically-exposed mice (NTP 1989). The lung hyperplasia was seen in all groups of mice exposed for 103 weeks, in males at doses of 60 and 120 mg/kg/day and in females at doses of 120 and 240 mg/kg/day (NTP 1989). The hyperplasia occurred in bronchiolar epithelial cells, often extending into the alveolar ducts (NTP 1989).

Nasal hyperplasia was observed in both control and chemically-treated mice in a 103-week study (NTP 1989). The hyperplasia was associated with inflammation from foreign material (corn oil, hair, and particles of feed and bedding) lodged in the nasal cavity, and the effect of oral 2,3-benzofuran exposure was to increase the inflammatory response to such particles, particularly at the highest dose tested in females, 240 mg/kg/day (NTP 1989).

Cardiovascular Effects. Histological examination of the heart and circulatory system of rats and mice exposed to 2,3-benzofuran by gavage for up to 2 years showed a compound-related increase in mineralization of the pulmonary artery in chronically-exposed rats (NTP 1989). The NOAEL values for cardiovascular effects are identified as the highest doses for which histological examinations were performed (250 mg/kg/day for acute-duration exposure and 500 mg/kg/day for intermediate-duration exposure). artery mineralization, Pulmonary nephropathy, which was considered secondary to increased severity of was seen only in the low-dose groups of rats exposed for 103 weeks (30 mg/kg/day in male rats and 60 mg/kg/day in female rats) (NTP 1989). The lack of effect at the higher doses was attributed to reduced survival (NTP 1989).

Gastrointestinal Effects. Histological examination of stomach and intestines of rats and mice with acute- or intermediate-duration exposure to 2,3-benzofuran by gavage showed no compound-related lesions, but chronic exposure caused forestomach hyperplasia in rats and mice (NTP 1989). Male rats exposed for 103 weeks had a significant increase in chronic inflammation of the forestomach at a dose of 30 mg/kg/day, and significant increases in

epithelial hyperplasia and ulcers at a dose of 60 mg/kg/day (NTP 1989). In mice exposed for 103 weeks, forestomach hyperplasia was increased in males at the higher dose (120 mg/kg/day) but not at the lower dose (60 mg/kg/day), and was increased in females in both dose groups (120 and 240 mg/kg/day) (NTP 1989). Only the increase at 120 mg/kg/day in female mice was statistically significant (NTP 1989).

Hematological Effects. Histological examination of tissues from the hematopoietic system of rats and mice exposed to 2,3-benzofuran by gavage for up to 2 years showed no compound-related lesions at the highest doses examined (250 mg/kg/day for acute-duration exposure, 500 mg/kg/day for intermediate-duration exposure, and 120 mg/kg/day in rats and 240 mg/kg/day in mice for chronic-duration exposure) (NTP 1989). Effects of oral exposure to 2,3-benzofuran on hemoglobin, hematocrit, red blood cells, white blood cells, or other hematological parameters have not been examined in any reported study. The NOAEL values for hematological effects for each species and duration category are presented in Table 2-1 and Figure 2-1.

Musculoskeletal Effects. Histological examination of tissues from the musculoskeletal system of rats and mice exposed to 2,3-benzofuran by gavage for up to 2 years showed a compound-related increase in bone degeneration (fibrous osteodystrophy) in chronically-exposed male rats (NTP 1989). The observed increase in bone degeneration, which was not statistically significant at doses of either 30 or 60 mg/kg/day, was not considered a direct effect of 2,3-benzofuran exposure, but as secondary to calcium and phosphate imbalance due to increased severity of nephropathy in male rats caused by 2,3-benzofuran exposure (NTP 1989).

Hepatic Effects. The liver is a common target organ for substituted furan compounds (Boyd 1981). Ten days of oral exposure of female mice to a dose of 591 mg/kg/day of 2,3-benzofuran altered the activity of several hepatic enzymes, decreasing the rate of reactions which activate electrophiles and increasing the rate of reactions which deactivate electrophiles (Cha et al. 1985; Heine et al. 1986). No toxicity was reported in this study (Cha et al. 1985; Heine et al. 1986). Liver damage was seen in rats exposed to 2,3-benzofuran by gavage for 13 weeks and in mice exposed for 103 weeks (NTP 1989). Necrosis of individual hepatocytes was observed after 13 weeks of exposure to 2,3-benzofuran in male rats at doses of 125, 250, and 500 mg/kg/day and in female rats at doses of 250 and 500 mg/kg/day (NTP 1989). No histology was performed on rats exposed at lower doses so confidence in 125 mg/kg/day as a LOAEL for liver damage is low and no NOAEL can be established. Cells resembling normal hepatocytes were found adjacent to and within the pancreatic islets of female rats exposed to 120 mg/kg/day of 2,3-benzofuran for 103 weeks, but these cells were considered to have arisen by transdifferentiation of pancreatic cells (NTP 1989). This metaplasia of the pancreatic islets was not accompanied by any other adverse histologic changes (NTP 1989). The incidence of multinuclear hepatocytes was increased in the livers of male mice exposed to 2,3-benzofuran for 103 weeks at doses of 60 and 120 mg/kg/day (NTP 1989); since this effect was seen at the lowest dose tested, no threshold can be determined.

Renal Effects. The kidney appears to be the organ most consistently affected by 2,3-benzofuran. Male Fisher F344/N rats have a high incidence of spontaneous nephropathy, characterized by degeneration, necrosis, and mineralization of tubular cells, and this nephropathy was made more severe by intermediate- and chronic-duration exposure to 2,3-benzofuran (NTP 1989). The increased severity of nephropathy was accompanied by additional effects in chemically-treated rats, including cortical cysts, bone degeneration, hyperplasia of the parathyroid glands and pelvic epithelium, and mineralization of the pulmonary artery (NTP 1989). Among male rats exposed for 13 weeks, increased severity of nephropathy was seen at a dose of 250 mg/kg/day but not at lower doses. Among male rats exposed for 103 weeks, increased severity of nephropathy contributing to reduced survival was seen at both doses tested, 30 and 60 mg/kg/day.

Female rats had a statistically-significant increase in nephropathy following 13 weeks of exposure to 2,3-benzofuran at doses of 250 and 500 mg/kg/day, but not at 125 mg/kg/day, and exhibited increased severity of nephropathy following 103 weeks of exposure at both doses tested, 60 and 120 mg/kg/day (NTP 1989). Female rats developed renal tubular cell atypical hyperplasia following 103 weeks of exposure to a dose of 120 mg/kg/day (NTP 1989). Male mice exhibited kidney lesions (tubular cell necrosis, inflammation, and focal mineralization) after 13 weeks of 2,3-benzofuran exposure at a dose of 250 mg/kg/day, but not at lower doses for 13 weeks or at doses of 60 or 120 mg/kg/day for 2 years (NTP 1989). No kidney damage was found in female mice at any duration or dose of 2,3-benzofuran, up to 250 mg/kg/day for 14 days, up to 500 mg/kg/day for 13 weeks, or up to 240 mg/kg/day for 2 years (NTP 1989). The highest NOAEL values and all reliable LOAEL values for renal effects for each species and duration category are presented in Table 2-1 and Figure 2-1.

Dermal/Ocular Effects. Histological examination of the skin and eyes of rats and mice exposed to 2,3-benzofuran by gavage for up to 2 years showed no compound-related lesions at the highest doses examined (250 mg/kg/day for acute-duration exposure, 500 mg/kg/day for intermediate-duration exposure, and 120 mg/kg/day in rats and 240 mg/kg/day in mice for chronic-duration exposure) (NTP 1989). Rats exposed to oral doses of 500 and 1,000 mg/kg/day of 2,3-benzofuran for 3-14 days exhibited a red ocular discharge, but this discharge was not characterized and no histological examinations were performed on animals in these dose groups (NTP 1989).

Other Systemic Effects. Oral 2,3-benzofuran exposure resulted in decreased body weights in some cases (NTP 1989). In rats, reduced body weight was observed after 14 days of exposure of males at doses of 250 and 500 mg/kg/day and of females at a dose of 500 mg/kg/day, after 13 weeks of exposure of males at doses of 125, 250, and 500 mg/kg/day and of females at a dose of 500 mg/kg/day, and after 103 weeks of exposure of males at doses of 30 and 60 mg/kg/day and of females at a dose of 120 mg/kg/day (NTP 1989). In mice, reduced body weight was observed after 13 weeks of exposure of males at a dose of 500 mg/kg/day, and after 103 weeks of exposure of males at a dose of 60 mg/kg/day but not 120 mg/kg/day and of females at doses of 120 and

240 mg/kg/day (NTP 1989). No explanation was provided for the reduction in body weight in male mice in the low dose group but not the high dose group during chronic exposure (NTP 1989). Body weight reduction does not provide specific information concerning toxicity, and often occurs only at doses above those causing other systemic effects. The relative sensitivity to body-weight reduction does appear to parallel the sensitivity to kidney and liver damage: male rats are most sensitive, followed by female rats, male mice, and female mice (NTP 1989).

Rats exposed to 2,3-benzofuran for 13 weeks had an increased incidence of cytoplasmic vacuolization of the adrenal glands, which was observed in 1 out of 10 control males, 2 out of 10 males at a dose of 250 mg/kg/day, and in all 20 males and females at a dose of 500 mg/kg/day (NTP 1989). No adrenal lesions were seen in rats at shorter or longer exposures, and no tests were made to determine the effect on adrenal functioning.

In rats exposed to 2,3-benzofuran for 103 weeks, the occurrence of cystic follicles in the thyroid glands was increased in males at doses of 30 and 60 mg/kg/day but decreased in females at doses of 60 and 120 mg/kg/day (NTP 1989). Parathyroid hyperplasia was increased in male rats exposed for 103 weeks to a dose of 30 mg/kg/day, secondary to increased severity of nephropathy (NTP 1989).

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans after oral exposure to 2,3-benzofuran. No abnormalities in lymphatic tissues were detected by histological examination of rats and mice exposed to 2,3-benzofuran by gavage for up to 2 years (NTP 1989). However, no examination of lymphocytes or tests of immune system functioning were made, so these studies do not identify a reliable NOAEL for immunological effects.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to 2,3-benzofuran. No abnormalities in the nervous systems were detected by histopathologic examination of rats and mice exposed to 2,3-benzofuran for up to 2 years (NTP 1989). However, no neurochemical or neurophysiological parameters were monitored, so these studies do not identify a reliable NOAEL for neurological effects.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after oral exposure to 2,3-benzofuran.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to 2,3-benzofuran. No damage to male or female reproductive organs was detected by histological examination of rats and mice exposed to 2,3-benzofuran by gavage for up to 2 years (NTP 1989). However, no functional tests of reproductive success have been made, so these studies do not identify a reliable NOAEL for reproductive effects.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to 2,3-benzofuran. Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans after oral exposure to 2,3-benzofuran. Chronic gavage exposure to 2,3-benzofuran increases the frequency of tumors in several organs in rats and mice (NTP 1989). In rats, a statistically-significant increase in kidney adenocarcinomas was found in females at a dose of 120 mg/kg/day, but no carcinogenic effects were seen in males, perhaps because of reduced survival (NTP 1989). In mice, increased frequencies of tumors were found in lungs, livers, and forestomachs of both males and females (NTP 1989). Most of these effects showed a dose-response trend and were statistically significant at both doses tested, 60 and 120 mg/kg/day in males and 120 and 240 mg/kg/day in females (NTP 1989). The NTP concluded that the data provided no evidence of carcinogenicity of 2,3-benzofuran to male rats, some evidence of carcinogenicity to female rats, and clear evidence of carcinogenicity to male and female mice (NTP 1989).

Levels of exposure associated with the observed carcinogenic effects of 2,3-benzofuran are indicated in Figure 2-l. Cancer effects could occur at lower exposure levels, but no estimate of the individual human lifetime cancer risks from exposure to 2,3-benzofuran has been made at this time by the EPA.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to 2,3-benzofuran.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to 2,3-benzofuran.

Dermal/Ocular Effects. No skin lesions or dermatitis were reported in an early review of the dermatological problems associated with the manufacture of coumarone-indene resin (a polymer made from 2,3-benzofuran and indene); however, the manufacturing process essentially prevented contact with monomers (Schwartz 1936), so the significance of these negative findings is questionable. Workers continuously exposed to wood varnished with coumarone-indene resin developed dermatitis, but the sensitivity was attributed to the sulfuric acids in the varnish (Schwartz 1936).

No studies were located regarding the following health effects in humans or animals after dermal exposure to 2,3-benzofuran:

2.2.3.3 Immunological Effects
2.2.3.4 Neurological Effects
2.2.3.5 Developmental Effects
2.2.3.6 Reproductive Effects
2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to 2,3-benzofuran. Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to 2,3-benzofuran.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure .

No studies were located regarding absorption in humans or animals after inhalation exposure to 2,3-benzofuran. The partitioning of 2,3-benzofuran between particulate matter and synthetic alveolar surfactant in vitro was reported to depend upon the chemical nature of the particles (Sehnert and Risby 1988). Synthetic lung surfactant was able to dissolve 2,3-benzofuran adsorbed to particles with few active sites, but not 2,3-benzofuran adsorbed to particles with many active sites (Sehnert and Risby 1988). These data indicate that inhalation of particles containing 2,3-benzofuran would result in some absorption, depending on the nature of the particles.

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans or animals after oral exposure to 2,3-benzofuran.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans or animals after dermal exposure to 2,3-benzofuran.

2.3.2 Distribution

No studies were located regarding distribution in humans or animals after exposure to 2,3-benzofuran by the following routes:

2.3.2.1 Inhalation Exposure
2.3.2.2 Oral Exposure
2.3.2.3 Dermal Exposure

2.3.3 Metabolism

No studies were located regarding metabolism of 2,3-benzofuran in humans or animals. However, the metabolism of several other substituted furans has been shown to involve oxidation by P-450, with the unsubstituted double bond of the furan ring converted either to an epoxide (Boyd 1981) or to a dialdehyde (Ravindranath et al. 1984). Pretreatment with inducers and inhibitors of P-450 modified the toxicity of a single intraperitoneal injection of 2,3-benzofuran to male mice (McMurtry and Mitchell 1977). Oral exposure to 2,3-benzofuran altered the activity of P-450 and other enzymes in the livers of female mice (Heine et al. 1986). These experiments indicate that cytochrome P-450 may be involved in the toxicity of 2,3-benzofuran, but do not provide a clear picture of 2,3-benzofuran metabolism.

2.3.4 Excretion

No studies were located regarding excretion in humans or animals after exposure to 2,3-benzofuran by the following routes:

2.3.4.1 Inhalation Exposure
2.3.4.2 Oral Exposure
2.3.4.3 Dermal Exposure

2.4 RELEVANCE TO PUBLIC HEALTH

As discussed in Section 2.2, estimates of levels of exposure to 2,3-benzofuran posing minimal risk to humans (MRLs) were to have been made, where data were believed reliable, for the most sensitive noncancer effect for each route and exposure duration. However, no MRLs could be derived for 2,3-benzofuran. No data were located on effects of acute-duration, intermediate-duration, or chronic-duration inhalation exposure to 2,3-benzofuran in humans or animals. Therefore, no inhalation MRLs were derived. Available information on acute-duration oral exposure in animals does not identify the most sensitive effect or any dose-response relationships (NTP 1989). Available information on intermediate-duration and chronic duration oral exposure to 2,3-benzofuran in animals suggests that the most

sensitive effect may be liver toxicity following intermediate-duration exposure and kidney toxicity following chronic-duration exposure (NTP 1989), but the data do not reliably identify the threshold for liver or kidney damage. Therefore, no oral MRLs were derived. Acute-duration, intermediate duration, and chronic-duration dermal MRLs were not derived for 2,3-benzofuran due to the lack of an appropriate methodology for the development of dermal MRLs.

Essentially nothing is known about the effects of 2,3-benzofuran exposure on humans. The principal adverse health effects noted in animals associated with oral exposure to 2,3-benzofuran are kidney and liver damage (NTP 1989). Intraperitoneal injection of 2,3-benzofuran also causes kidney and liver damage (McMurtry and Mitchell 1977). Inhalation and dermal exposures might also produce adverse effects, although this has not been studied. Because of the limited production and use of 2,3-benzofuran (see Chapter 4), the average person is unlikely to encounter doses high enough to cause kidney or liver damage. However, studies in animals indicate that 2,3-benzofuran exposure may increase the risk of cancer (NTP 1989), and so even low exposure levels may be of concern. Kidney and liver damage, cancer, and other less common effects are discussed in greater detail below.

Death. Large oral doses of 2,3-benzofuran can cause death in rats or mice following acute or intermediate exposure duration, and somewhat lower chronic doses can reduce survival (NTP 1989). No consistent difference in sensitivity between male and females has been observed (NTP 1989). The lethality of 2,3-benzofuran exposure by intraperitoneal injection appears to be greater than that following gavage exposure, as a single intraperitoneal injection of 100 mg/kg caused deaths in some male mice (McMurtry and Mitchell 1977), but 14-day gavage exposure caused no deaths in rats or mice at doses up to 250 mg/kg/day (NTP 1989). The cause of death from 2,3-benzofuran exposure was not reported in these studies except that reduced survival in male rats chronically exposed to 2,3-benzofuran was attributed to increased severity of kidney damage (NTP 1989). An acute dose of 240 mg/kg/day caused death in male mice in a group which had been exposed to 60 mg/kg/day for 20 weeks, but an acute dose of 250 mg/kg/day for 14 days caused no deaths in mice which had not previously been exposed to 2,3-benzofuran (NTP 1989). Although no data were provided concerning the cause of increased lethality of 2,3-benzofuran following prior exposure, cumulative organ damage or altered metabolism are possible explanations. It is unlikely that humans would be exposed to a dose of 2,3-benzofuran sufficient to cause death.

Systemic Effects.

Respiratory Effects. Chronic-duration oral exposure to 2,3-benzofuran causes hyperplasia of nasal mucosa and lung tissue in mice (NTP 1989). In vitro exposure of chicken trachea cells to 2,3-benzofuran results in substantial inhibition of ciliary activity (Pettersson et al. 1982), which may indicate that ciliotoxicity is involved in the respiratory effects seen in mice. Certain other furan derivatives exhibit pulmonary toxicity due to metabolic activation by lung P-450 oxygenases (Boyd 1981), but 2,3-benzofuran

has not been studied specifically. No respiratory effects were seen following acute-, intermediate-, or chronic-duration oral exposure in rats or following acute- or intermediate-duration oral exposure in mice. Thus, respiratory effects are seen fairly infrequently, and only at high doses which also cause liver damage.

Cardiovascular Effects. Chronic-duration oral exposure to 2,3-benzofuran causes mineralization of the pulmonary artery in rats, but this effect was due to mineral imbalances and vascular constriction associated with kidney damage (NTP 1989). No cardiovascular effects were seen following acute-, intermediate-, or chronic-duration oral exposure in mice or following acute- or intermediate-duration oral exposure in rats.

Gastrointestinal Effects. Chronic-duration oral exposure to 2,3-benzofuran causes chronic inflammation of the forestomach in rats and mice (NTP 1989). No gastrointestinal effects were seen following acute- or intermediate-duration oral exposure in rats or mice. The gastrointestinal effects were seen at doses causing severe kidney damage or above doses causing liver damage.

Musculoskeletal Effects. Chronic-duration oral exposure to 2,3-benzofuran causes bone degeneration in rats, but this effect is due to mineral imbalances associated with kidney damage (NTP 1989). No musculoskeletal effects were seen following acute-, intermediate-, or chronic duration oral exposure in mice or following acute- or intermediate-duration oral exposure in rats.

Hepatic Effects. Liver damage is a consistent systemic effect of oral exposure to 2,3-benzofuran (NTP 1989). Intermediate-duration oral exposure causes liver damage in male and female rats and chronic-duration oral exposure causes liver damage in male mice (NTP 1989). Liver damage is also seen following a single intraperitoneal injection of 2,3-benzofuran (McMurtry and Mitchell 1977). The observed liver damage is usually characterized by focal necrosis of hepatocytes after both oral (NTP 1989) and intraperitoneal (McMurtry and Mitchell 1977) exposure. Liver damage was the systemic effect seen at the lowest dose in male rats exposed to 2,3-benzofuran for 13 weeks (NTP 1989).

The toxicity of 2,3-benzofuran to the liver may be associated with activation by P-450 oxygenases. Pretreatment of mice with an inhibitor of P-450 oxygenases, cobaltous chloride, prevents liver damage from intraperitoneal injection of 2,3-benzofuran (McMurtry and Mitchell 1977). Acute-duration oral exposure to 2,3-benzofuran alters the activity of hepatic enzymes in mice, decreasing the cytochrome P-450 content and increasing the activity of several enzymes involved in the deactivation of electrophiles (Cha et al. 1985; Heine et al. 1986). This overall shift in metabolism away from activation of potential carcinogens was taken to suggest that 2,3-benzofuran might have anticarcinogenic activity (Cha et al. 1985; Heine et al. 1986).

However, because chronic-duration exposure to 2,3-benzofuran increases the incidence of cancer in rodents, including liver cancer in mice (NTP 1989), any possible anticarcinogenic action of 2,3-benzofuran is less relevant.

Renal Effects. Intermediate- and chronic-duration oral exposure to 2,3-benzofuran causes kidney damage in male and female rats and intermediate-duration oral exposure causes kidney damage in male mice (NTP 1989). Intraperitoneal injection also causes kidney damage in male mice (McMurtry and Mitchell 1977). Kidney damage involves injury to the tubular cells, with degeneration, necrosis, and mineralization. In male rats (a group predisposed to kidney damage), chronic 2,3-benzofuran exposure increases the severity of the nephropathy to an extent which affects survival at a lifetime dose of 30 mg/kg/day (NTP 1989). Kidney damage seen in rats following chronic-duration oral exposure to 2,3-benzofuran also involved cortical cysts, bone degeneration, hyperplasia of the parathyroid glands and pelvic epithelium, and mineralization of the pulmonary artery (NTP 1989).

Other Systemic Effects. Oral exposure to 2,3-benzofuran causes decreased body weight in rats and mice, and damage to adrenal and thyroid glands in rats (NTP 1989). Reduced body weight is a rather unspecific indicator of toxicity, and was generally not seen except at doses also causing liver or kidney damage. Adrenal and thyroid lesions were seen infrequently, and there was no indication of an effect on organ function (NTP 1989).

The systemic effects caused by 2,3-benzofuran exposure which are most relevant to public health are liver and kidney damage. Other systemic effects, including damage to the adrenal and thyroid glands, lungs, and pancreas, and reduced body weight, are generally seen only at doses above those causing kidney or liver damage. High-level exposure to 2,3-benzofuran would be expected to damage the liver or kidney, and possibly other organs in some individuals.

Immunological Effects. Oral lifetime exposure to 2,3-benzofuran caused no histopathological lesions in lymphatic tissues of rats or mice (NTP 1989). This provides limited evidence that the immunological system may not be a major target for 2,3-benzofuran toxicity, but more definitive conclusions are not possible without further studies.

Neurological Effects. Oral lifetime exposure to 2,3-benzofuran caused no histopathological lesions in tissues of the nervous systems of rats or mice (NTP 1989). However, no tests of neurological function were performed, and so the significance of these negative findings with regard to public health cannot be evaluated.

Developmental Effects. No information is available concerning any effects on development from 2,3-benzofuran exposure.

Reproductive Effects. Oral lifetime exposure to 2,3-benzofuran caused no histopathological lesions in male or female reproductive organs of rats or mice (NTP 1989). However, no studies of organ function or reproductive success have been made, and so the potential effects of 2,3-benzofuran exposure on human reproduction cannot be evaluated.

Genotoxic Effects. No in vivo studies of 2,3-benzofuran genotoxicity were located. The genotoxicity of 2,3-benzofuran has been studied in a number of in vitro systems (Table 2-2). 2,3-Benzofuran was found not to be mutagenic to Salmonella tvphimurium, both with and without exogenous activation (Florin et al. 1980; Haworth et al. 1983; Weill-Thevenet et al. 1981). However 2,3-benzofuran does give positive responses in genotoxicity assays for mutagenicity to mouse lymphoma L5178Y cells (McGregor et al. 1988) and for sister chromatid exchanges in Chinese hamster ovary cells (NTP 1989). Limited evidence suggests that 2,3-benzofuran could be metabolized to an electrophilic epoxide or dialdehyde (see Section 2.3.3), and such an intermediate would be an alkylating agent capable of reacting with DNA. Thus, one possible explanation for the mixed genotoxicity results is differences among the metabolic conditions used in the various tests.

Cancer. 2,3-Benzofuran is carcinogenic to rats and mice (NTP 1989). Chronic oral exposure increased the incidence of kidney tumors in female rats, and increased the incidence of lung, forestomach, and liver tumors in male and female mice (NTP 1989). These findings indicate that chronic exposure to 2,3-benzofuran could be a cause of concern even at low levels; however, without more extensive exposure data, it is not possible to characterize the magnitude of human cancer risk from 2,3-benzofuran exposure.

No information is available concerning the mechanism of carcinogenicity of 2,3-benzofuran. All of the tissues showing a carcinogenic response also exhibited hyperplasia, but there was no evidence that neoplasia was a progression from hyperplasia (NTP 1989). Substituted furans can be activated by cytochrome P-450 to electrophilic intermediates (epoxides or dialdehydes) (Boyd 1981; Ravindranath et al. 1984), and furan and furfural can activate oncogenes in mouse liver (NTP 1989; Reynolds et al. 1987); however, the metabolism of 2,3-benzofuran has not been specifically studied. A possible mechanism for the carcinogenicity of 2,3-benzofuran is electrophilic attack on DNA. The evidence that 2,3-benzofuran has only limited genotoxicity in vitro (see Table 2-2) could be the result of inadequate metabolic activation.

2.5 BIOMARRERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the

TABLE 2-2. Genotoxicity of 2,3-Benzofuran In Vitro

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium (plate incorporation)	Gene mutation	-	-	Weill-Thevenet et al. 1981
S. typhimurium (liquid preincubation)	Gene mutation	-	-	Florin et al. 1980
S. typhimurium (liquid preincubation)	Gene mutation	-	-	Haworth et al. 1983
Mammalian cells:				
Mouse lymphoma L5178Y thymidinekinase locus	Gene mutation	No data	+	McGregor et al. 1988
Chinese hamster ovary	Chromosomal aberrations	-	-	NTP 1989
Chinese hamster ovary	Sister chromatid exchange	+	+	NTP 1989

+ = positive result; - = negative result

substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 2,3-benzofuran are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 2,3-benzofuran are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to 2,3-Benzofuran

2,3-Benzofuran has been detected in samples of breast milk (Pellizzari et al. 1982) and in blood from victims who died in fires (Anderson and Harland 1980), but no information was provided by either study on previous exposure to 2,3-benzofuran. No information was located concerning metabolites of 2,3-benzofuran in animals or humans. No information was located concerning the fate of 2,3-benzofuran in animals or humans, so it is not possible to predict how long 2,3-benzofuran remains in the body, or how body levels might correlate with exposure or effects.

2.5.2 Biomarkers Used to Characterize Effects Caused by 2,3-Benzofuran

No information is available concerning the effects of 2,3-benzofuran in humans. Acute oral exposure to 2,3-benzofuran has been shown to alter levels of enzyme activity in the livers of female mice (Heine et al. 1986), but much more work would need to be done to determine whether there is a pattern of enzyme alteration specific to 2,3-benzofuran exposure. Other effects found in animals following oral exposure to 2,3-benzofuran are kidney and liver damage and kidney, lung, liver, and stomach cancer (see Section 2.2.2). Such generalized responses do not suggest the basis for any specific biomarker of clinical or preclinical effects caused by 2,3-benzofuran.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Pretreatment of male mice with compounds that affect cytochrome P-450 oxygenases altered the toxicity of a single intraperitoneal injection of 2,3-benzofuran (McMurtry and Mitchell 1977). However, kidney necrosis was decreased both by phenobarbital, which induces P-450, and by cobaltous chloride and piperonyl butoxide, which inhibit P-450. Also, one of the P-450 inhibitors, cobaltous chloride, decreased lethality while the other, piperonyl butoxide, increased lethality. Differential effects on liver and kidney P-450 systems could explain some of these observations. Compounds which affect P-450 metabolism are likely to alter 2,3-benzofuran toxicity, but the effects on P-450 are not predictive of the specific effects on 2,3-benzofuran toxicity.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Studies of 2,3-benzofuran toxicity in animals reveal differences in susceptibility between sexes and between species, with male rats being the most sensitive (see Section 2.2). Male rats have a high rate of spontaneous kidney disease, and their greater sensitivity to 2,3-benzofuran toxicity may be because the target organ is already damaged. Although no studies provide data concerning human susceptibility, it is reasonable to assume that persons with kidney or liver disease would be more susceptible to the toxic effects of 2,3-benzofuran. In addition, people who have altered P-450 metabolism, due to disease, alcoholism, age, or exposure to drugs or chemicals, would be expected to have altered 2,3-benzofuran toxicity (see Section 2.3.3), but the extent or the direction of the effect (protective or harmful) cannot be predicted.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 2,3-benzofuran. However, because some of the treatment discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 2,3-benzofuran. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Human exposure to 2,3-benzofuran can occur by inhalation, ingestion, or by dermal contact. Also, 2,3-benzofuran has been detected in human milk and can thus be transferred to a nursing infant (Pellizzari et al. 1982). Essentially nothing is known about the effects of 2,3-benzofuran exposure on humans. No information was located on treatment for 2,3-benzofuran specifically, but the sources listed below provided information for the general class of "phenols" and indicated that this information applied to 2,3-benzofuran exposure; however, it is not known if all of this information applies to 2,3-benzofuran exposure. General recommendations for reducing adsorption following acute exposure have included removal of the chemical with undiluted polyethylene glycol prior to washing with large quantities of water (HSDB 1992). If the eyes have been exposed, irrigation with copious amounts of tepid water has been suggested (HSDB 1992). If ingestion has occurred, gastric lavage may be indicated if performed soon after ingestion, or in patients who are comatose or at risk of convulsing (HSDB 1992). Administration of activated charcoal slurry, aqueous or mixed with saline cathartic or sorbitol has also been suggested (HSDB 1992). Diazepam may be helpful in controlling seizures (HSDB 1992).

Very little data is available on the retention of 2,3-benzofuran. Synthetic lung surfactant was able to dissolve 2,3-benzofuran adsorbed to some particles (Sehnert and Risby 1988), suggesting that it may be absorbed through the lungs. Some substituted furans have been shown to be metabolized by the P-450 enzyme system (Boyd 1981; Ravindranath et al. 1984), suggesting that this is a likely metabolic route for 2,3-benzofuran as well. Certain drugs, such as cobaltous chloride and piperonyl butoxide, inhibit this enzyme system, and were shown to alter the liver and kidney toxicity of 2,3-benzofuran (McMurtry and Mitchell 1977). However, not all treatments with inhibitors and inducers of the P-450 system gave the expected results in this study. One possible explanation for these discrepancies could be the differential effects on the different P-450 systems. It is possible that one or more drugs with this activity could be developed and used to inhibit metabolism of 2,3-benzofuran to more toxic metabolites.

Little is known about the effects of 2,3-benzofuran exposure on humans. The principal adverse health effects noted in animals associated with oral exposure to 2,3-benzofuran are kidney and liver damage (NTP 1989). In the kidney, 2,3-benzofuran causes injury to the tubular cells, with degeneration, necrosis, and mineralization. In the liver, damage due to 2,3-benzofuran is usually characterized by focal necrosis of hepatocytes. However, the mechanism(s) associated with this damage are unknown. A better understanding of the mechanism of action of 2,3-benzofuran may make it possible to develop effective methods to reduce toxic effects caused by exposure.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consulXation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 2,3-benzofuran 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 2,3-benzofuran.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of 2,3-Benzofuran

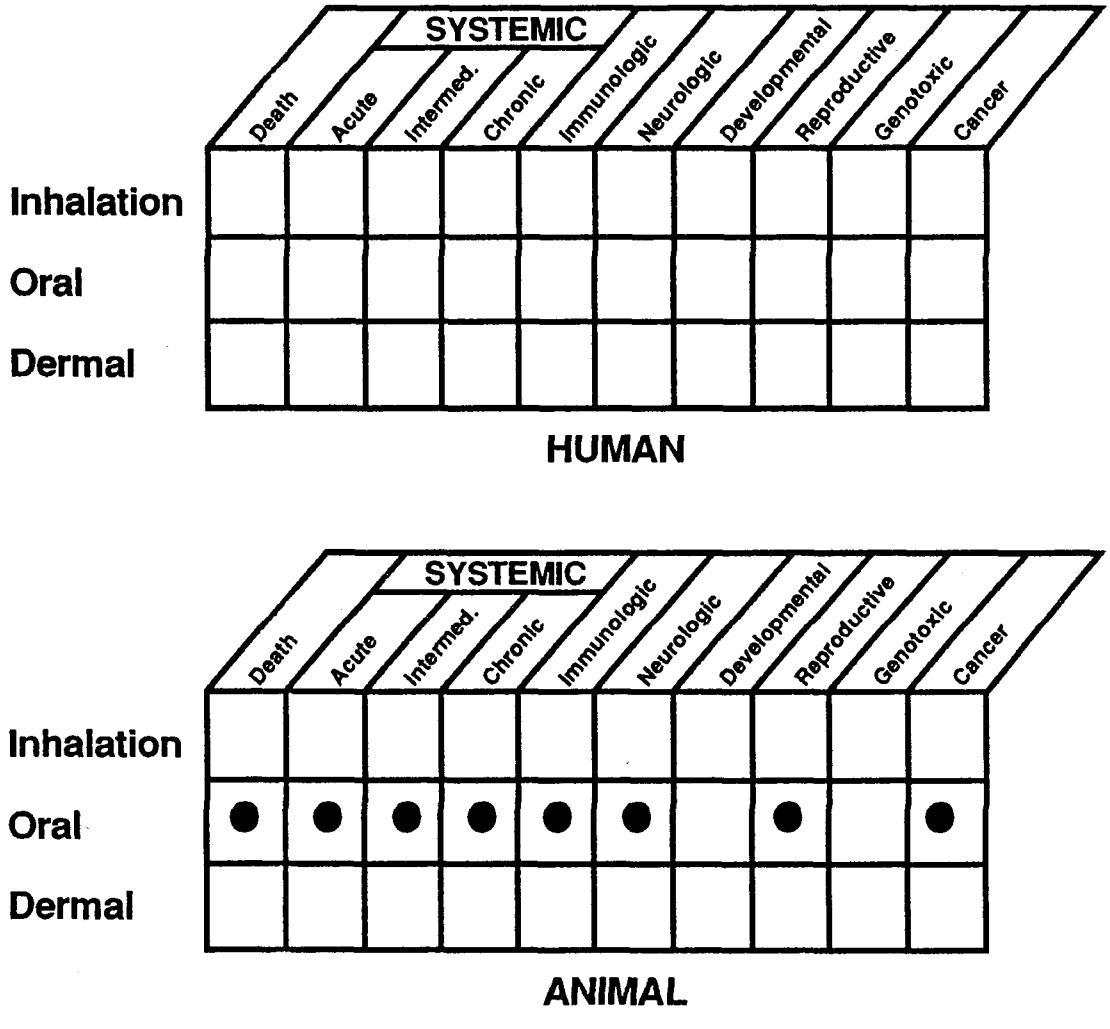
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 2,3-benzofuran are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of 2,3-benzofuran. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

No data exist on the health effects of 2,3-benzofuran in humans. No data exist on the health effects of 2,3-benzofuran in animals following inhalation or dermal exposure. Information on the health effects in rats and mice following oral exposure to 2,3-benzofuran comes primarily from a well-conducted gavage study by NTP of acute-, intermediate-, and chronic-duration (NTP 1989). However, this NTP study was limited to examining histopathological endpoints, so information on immunologic, neurologic and reproductive effects does not include evidence concerning organ or system function. In addition, developmental and in vivo genotoxic effects of 2,3-benzofuran exposure have not been studied.

2.9.2 Data Needs

Acute-Duration Exposure. No data are available on the effects of acute-duration exposure to 2,3-benzofuran in humans. No data are available on the effects of 2,3-benzofuran in animals following inhalation and dermal exposure. Lethality in rats was reported in the NTP gavage study but the cause of death was not known. The only systemic effects observed were red ocular and nasal discharges and decreased body weights (NTP 1989). Lethality as well as kidney and liver damage were seen in mice following a single intraperitoneal injection of 2,3-benzofuran (McMurtry and Mitchell 1977). Currently, little or no information is available concerning the target organ or the dose-response of toxicity following inhalation, oral, or dermal exposure, and no oral or inhalation MRLs could be derived. Toxicokinetic data for acute-duration exposure are insufficient to identify targets or to allow conclusions to be made across routes of exposure. Such data are unlikely to become available from human studies, but establishing the end points and levels

FIGURE 2-2. Existing Information on Health Effects of 2,3-Benzofuran



causing toxicity from acute exposure of animals to 2,3-benzofuran by all three routes would be useful to evaluate risk to populations surrounding hazardous waste sites who might be exposed to 2,3-benzofuran for brief periods.

Intermediate-Duration Exposure. No data are available on the effects of intermediate-duration exposure to 2,3-benzofuran in humans. No information is available on the effects of 2,3-benzofuran in animals following inhalation or dermal exposure of intermediate duration, and no inhalation MRL could be derived. Histological evidence of liver damage in male rats exposed to 2,3-benzofuran by gavage for 13 weeks was reported in the lowest dose group examined (125 mg/kg/day) (NTP 1989). Thus, no threshold for liver damage was established by these studies and no oral MRL could be calculated. No renal effects were observed in rats or mice at the dose causing necrosis of liver cells in male rats, but kidney damage was observed at the next higher dose tested, 250 mg/kg/day, in rats and mice (NTP 1989). Studies to establish an oral MRL would be helpful in evaluating risk to populations near hazardous waste sites who might be exposed to 2,3-benzofuran for intermediate durations. Such studies would be valuable if they included examination of liver and kidney function in addition to histopathology. Toxicokinetic data for intermediate-duration exposure are insufficient to identify targets or to allow conclusions to be made across routes of exposure. As for acute-duration exposure, human data are unlikely to become available, but go-day animal studies using several doses and investigating a number of end points would be helpful for assessing the levels which may cause health effects in humans following inhalation or dermal exposure to 2,3-benzofuran.

Chronic-Duration Exposure and Cancer. No data are available on the effects of chronic-duration exposure to 2,3-benzofuran in humans. The NTP study of oral exposure established the kidney as the most sensitive target organ in rats (NTP 1989), but no oral MRL could be derived because the kidney damage in male rats at the lowest dose used, 30 mg/kg/day, was too severe to establish a threshold. Studies using lower doses would establish a LOAEL for less serious effects and a NOAEL, which could also be better defined by tests of kidney function as well as histopathology. Currently, no information is available concerning the target organ or the dose-response of toxicity following inhalation or dermal exposure, and no inhalation MRL could be derived. Toxicokinetic data are insufficient to identify targets or to allow conclusions to be made across routes of exposure. Such information would be useful to evaluate risks to population near hazardous waste sites who might be exposed to 2,3-benzofuran for long periods of time. As for acute- and intermediate-duration exposure, human data are unlikely to become available, but animal studies would help define levels expected to cause adverse health effects in humans chronically exposed to 2,3-benzofuran by oral, inhalation, and dermal routes.

No epidemiologic studies were located concerning the potential human carcinogenicity of 2,3-benzofuran. Lifetime oral exposure increases cancer incidence in female rats and in male and female mice (NTP 1989). The carcinogenicity in both sexes and both species, as well as in multiple organs, strengthens the likelihood of a carcinogenic potential in humans. Studies of

the carcinogenicity of 2,3-benzofuran by inhalation or dermal exposure would be useful if toxicokinetic studies were to show substantial route-specific differences in absorption, distribution, metabolism, or excretion.

Genotoxicity. No data are available on the genotoxicity of 2,3-benzofuran in humans or animals. Genotoxicity results in vitro are mixed, with negative results in the most widely used genotoxicity test, S. tvphimurium mutagenicity (Florin et al. 1980; Haworth et al. 1983; McGregor et al. 1988; NTP 1989; Weill-Thevenet et al. 1981). Other substituted furans appear to be activated by P-450 oxygenases to epoxide (Boyd 1981) or dialdehyde (Ravindranath et al. 1984) intermediates, which are electrophilic and hence likely to react with DNA; however, the metabolism of 2,3-benzofuran has not been studied. The mixed genotoxicity in vitro could reflect inadequate activation, and so additional studies of in vivo metabolism and genotoxicity in animals (e.g., 32P post-labeling to detect DNA adducts following exposure to 2,3-benzofuran) would be useful to confirm or refute the genotoxic potential of 2,3-benzofuran.

Reproductive Toxicity. No data are available on the reproductive toxicity of 2,3-benzofuran in humans. No histopathologic lesions were reported in male or female reproductive organs in rats or mice following acute-, intermediate-, or chronic-duration oral exposure to 2,3-benzofuran (NTP 1989). However, no tests of organ function or reproductive success were done. Thus, limited data indicate that the reproductive system may not be a major target for 2,3-benzofuran toxicity, but further studies in animals by all three routes of exposure examining reproductive organ pathology and organ functions would be useful for assessing the possible effects of 2,3-benzofuran exposure on human reproduction.

Developmental Toxicity. No data are available on the developmental toxicity of 2,3-benzofuran in humans or animals. Thus, a complete investigation of the effects of 2,3-benzofuran on development, studying one rodent and one nonrodent species exposed by all three routes, would be useful to evaluate potential developmental toxicity in humans.

Immunotoxicity. No data are available on the immunotoxicity of 2,3-benzofuran in humans. No histopathologic abnormalities in lymphatic tissues of rats or mice were found following acute-, intermediate-, or chronic-duration oral exposure to 2,3-benzofuran (NTP 1989), indicating that the immune system may not be a target for 2,3-benzofuran toxicity. However, a battery of immune function tests has not been performed. A more thorough investigation could begin by examining peripheral lymphocytes in exposed animals, followed by more detailed studies if effects were found.

Neurotoxicity. No data are available on the neurotoxicity of 2,3-benzofuran in humans. No histopathologic lesions were noted in the nervous systems of rats or mice following acute-, intermediate-, or chronic-duration oral exposure to 2,3-benzofuran (NTP 1989), but no neurochemical or neurophysiological parameters were monitored. It would be helpful to conduct

neurological tests on animals exposed to 2,3-benzofuran by all three routes to establish if the nervous system may be a target for 2,3-benzofuran toxicity.

Epidemiological and Human Dosimetry Studies. No epidemiological or human dosimetry studies on the effects of 2,3-benzofuran were located. Production of coumarone-indene resin involves potential exposure to 2,3-benzofuran (Powers 1980), and so an occupationally exposed subpopulation could be identified. Animal studies suggest that kidney and liver damage and increased risk of cancer would be end points of concern (NTP 1989). Potential difficulties with epidemiological investigations include a small cohort of exposed workers, the difficulty of defining exposure levels, and the possibility that exposure to other chemicals could confound the results. Information from epidemiological and human dosimetry studies would be useful in establishing cause/effect relationships and in planning future monitoring of individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect. The presence of 2,3-benzofuran has been detected in breast milk (Pellizzari et al. 1982) and in blood from victims who died in fires (Anderson and Harland 1980), indicating that the concentration of 2,3-benzofuran in biological samples could serve as a biomarker of exposure. However, more studies on absorption, distribution, metabolism, and excretion would be useful to determine the lifetime of 2,3-benzofuran in the body and to correlate levels with duration and degree of exposure. Indirect evidence suggests that 2,3-benzofuran may be activated by P-450 oxygenases to an epoxide or dialdehyde intermediate which could react with cellular components (Heine et al. 1986; McMurtry and Mitchell 1977). Thus, an assay for adducts of 2,3-benzofuran in proteins or DNA could possibly be developed as a useful marker of exposure to 2,3-benzofuran.

The effects of 2,3-benzofuran exposure in humans are not known. Activities of enzymes in the liver are altered by acute exposure to 2,3-benzofuran in female mice (Heine et al. 1986), which suggests the possibility that there may be a specific response of serum enzyme levels to 2,3-benzofuran exposure that could be developed as a biomarker of effect. Other effects in animals include kidney and liver damage and an increased rate of kidney, lung, liver, and forestomach cancer (NTP 1989). Such effects are too general and severe to serve as biomarkers of 2,3-benzofuran effects.

Absorption, Distribution, Metabolism, and Excretion. No data are available on the absorption, distribution, metabolism, or excretion of 2,3-benzofuran in humans. Limited data suggest the involvement of P-450 oxygenases in the metabolism of 2,3-benzofuran in animals (Heine et al. 1986; McMurtry and Mitchell 1977), and further investigations would be valuable to define the role of organ-specific oxygenases in the toxicity and potential genotoxicity of 2,3-benzofuran. Absorption, distribution, and excretion in animals have not been studied at all via inhalation, oral, or dermal routes. Such information would be valuable because the relative rates and extent of absorption, distribution, metabolism, and excretion following exposure by different routes may account for differences in the toxicity of a chemical administered by different routes. These investigations could start with

monitoring levels as a function of exposure, by the inhalation, oral, and dermal routes, and at acute, intermediate, and chronic durations. It is likely that 2,3-benzofuran exists in the environment primarily adsorbed to particles (see Chapter 5), and the extent of desorption of 2,3-benzofuran by artificial lung surfactant in vitro depends on the nature of the particles (Sehnert and Risby 1988). Thus, studies of absorption would be most useful if they included exposure to 2,3-benzofuran on particles representative of those found in the environment.

Comparative Toxicokinetics. No data are available on toxicokinetics in animals or humans. There is some commonality of target organs (the kidney and liver) between rats and mice (NTP 1989), making it reasonable to assume that both species, and perhaps humans, would handle 2,3-benzofuran similarly. Establishing which animal species serves as the best model for extrapolating results to humans would be a useful first step in investigating comparative toxicokinetics.

Mitigation of Effects. No information was located concerning mitigation of effects of exposure to 2,3-benzofuran. Information on techniques to mitigate low-level, long-term effects would be useful in determining the safety and effectiveness of possible methods for treating 2,3-benzofuran exposed populations in the vicinity of hazardous waste sites.

2.9.3 On-going Studies

No information concerning research projects in progress to investigate 2,3-benzofuran was located.