

TOXICOLOGICAL PROFILE FOR
2,3-BENZOFURAN

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987; on October 20, 1988; on October 26, 1989; and on October 17, 1990. A revised list of 275 substances was published on October 17, 1991.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about 2,3-benzofuran and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). 2,3-Benzofuran has been found in at least 5 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for 2,3-benzofuran. As EPA evaluates more sites, the number of sites at which 2,3-benzofuran is found may change. This information is important for you to know because 2,3-benzofuran may cause harmful health effects and because these sites are potential or actual sources of human exposure to 2,3-benzofuran.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous chemical such as 2,3-benzofuran, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS 2,3-BENZOFURAN?

2,3-Benzofuran is a colorless, sweet-smelling, oily liquid which does not mix with water. 2,3-Benzofuran is made by processing coal into coal oil. 2,3-Benzofuran may also be formed during other uses of coal or oil. The part of the coal oil that contains 2,3-benzofuran is made into a plastic called coumarone-indene resin. Coumarone-indene resin can then be used to make paint, varnish, glue, and floor tiles, and it is allowed on food products and packages. We know very little about how 2,3-benzofuran might get into the environment or what happens to it after it gets there.

More information on the properties and uses of 2,3-benzofuran and how it behaves in the environment may be found in Chapters 3, 4, and 5.

1.2 HOW MIGHT I BE EXPOSED TO 2,3-Benzofuran?

2,3-Benzofuran has been found in a few places in the air and water. In most instances, when it was found; the amount that was there was not measured. We do not know what the levels of 2,3-benzofuran are in soil, air, water, or food. The reason that 2,3-benzofuran has not often been found could be that 2,3-benzofuran usually attaches to particles, and is not free in the air or water. We do not know where 2,3-benzofuran comes from, except when it is

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found near fuel-processing factories. Workers who make coal oil or coumarone-indene resin might be exposed to 2,3-benzofuran. Cigarette smoke has some 2,3-benzofuran in it. Coumarone-indene resin is allowed in food packages and as a coating on oranges and grapefruit. We do not know how often the resin is used or whether any 2,3-benzofuran in it gets into the food.

More information on how you might be exposed to 2,3-benzofuran is given in Chapter 5.

1.3 HOW CAN 2,3-BENZOFURAN ENTER AND LEAVE MY BODY?

We know very little about how 2,3-benzofuran can enter or leave your body. Some 2,3-benzofuran can enter your body from the environment if it is in the water that you drink, the food that you eat, or the air that you breathe. We do not know how much you would take in or when and how it would leave your body.

More information on how 2,3-benzofuran enters and leaves the body is given in Chapter 2.

1.4 HOW CAN 2,3-BENZOFURAN AFFECT MY HEALTH?

The effect of 2,3-benzofuran on your health depends on how much you take into your body. In general, the more you take in, the greater the chances that an effect will occur. No studies have been done to test the effects of 2,3-benzofuran on the health of humans. Studies in animals show that 2,3-benzofuran can damage the liver and kidneys if large amounts are given within a short time, and that very large amounts can kill. We do not know whether exposure to 2,3-benzofuran can affect your ability to have children or can harm an unborn baby.

Studies in animals show that exposure to 2,3-benzofuran at moderate levels over a long time can damage the liver, kidneys, lungs, and stomach. The brain, muscles, and heart do not seem to be seriously damaged by long-term exposure. Some rats and mice that received 2,3-benzofuran for their whole lives developed cancer of the kidney, lung, liver, or stomach. However, no cases of cancer in humans have been linked to exposure to 2,3-benzofuran. More information on the health effects of 2,3-benzofuran in humans and animals can be found in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 2,3-BENZOFURAN?

2,3-Benzofuran can be measured in your blood or in your milk if you are a nursing mother. The test is specific for 2,3-benzofuran but it requires special equipment and is not easily available. The test may only be able to detect 2,3-benzofuran for a certain period of time because it is not known how long 2,3-benzofuran remains in the body after you have been exposed to it.

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Also, the test only shows that you have been exposed; it cannot predict which health effects, if any, you will develop.

More information on how 2,3-benzofuran can be measured in exposed humans is given in Chapters 2 and 6.

1.6 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

No standards have been set for exposure to 2,3-benzofuran. The Food and Drug Administration specifies the quantity of coumarone-indene resin that may be used on food and in food packages.

More information on government regulations for 2,3-benzofuran can be found in Chapter 7.

1.7 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your state health or environmental department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

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 2-1. 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.

2. HEALTH EFFECTS

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 2-1 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) | | Reference |
|----------------------------|---------|-------|---------------------------------|-----------|----------------------|--------------------------------------|-------------------------|-----------|
| | | | | | | Less serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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) | | Reference |
|----------------------------|---------|-------|---------------------------------|---------------------------------------------------------------------|-----------------------------------------------|-----------------------------|-------------------------------------------------------------|-----------|
| | | | | | | Less serious (mg/kg/day) | Serious (mg/kg/day) | |
| Systemic | | | | | | | | |
| 7 | Rat | (GO) | 13 wk 5d/wk 1x/d | Resp Cardio Gastro Hemato Musc/skel Hepatic | 500 500 500 500 500 | | | NTP 1989 |
| | | | | Renal | 125 | 250 | (necrosis of hepatocytes in males) (tubular nephropathy) | |
| | | | | Derm/oc | 500 | | | |
| | | | | Other | 62.5 | 125 | (reduced body weight in males) | |
| 8 | Mouse | (GO) | 13 wk 5d/wk 1x/d | Resp Cardio Gastro Hemato Musc/skel Hepatic Renal | 500 500 500 500 500 500 125 | | | NTP 1989 |
| | | | | 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) | | Reference |
|----------------------------|---------|-------|---------------------------------|-----------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-----------|
| | | | | | | Less serious (mg/kg/day) | Serious (mg/kg/day) | |
| Systemic | | | | | | | | |
| 11 | Rat | (GO) | 103 wk 5d/wk 1x/d | Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc Other | 120 ^b 120 ^b 120 ^b 120 ^b 120 ^b | 30 (mineralization of pulmonary artery in males) 30 (forestomach inflammation in males) 30 (reduced body weight in males) | 30 (severe nephropathy in males) | NTP 1989 |
| 12 | Mouse | (GO) | 103 wk 5d/wk 1x/d | Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc Other | 240 ^c 60 240 ^c 240 ^c 240 ^c 240 ^c | 60 (lung hyperplasia in males) 120 (forestomach hyperplasia in females) 60 (multinuclear hepatocytes in males) 60 (reduced body weight in males) | | NTP 1989 |
| 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) | | Reference |
|----------------------------|---------|-------|---------------------------------|--------|----------------------|-----------------------------|---------------------------------------------------------|-----------|
| | | | | | | Less serious (mg/kg/day) | Serious (mg/kg/day) | |
| 14 | Mouse | (GO) | 103 wk 5d/wk 1x/d | | | 60 | CEL (lung, liver and forestomach tumors in males) | NTP 1989 |

^aThe number corresponds to entries in Figure 2-1.

^bNOAEL for effect in female rats. NOAEL in male rats is 60 mg/kg/day.

^cNOAEL 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

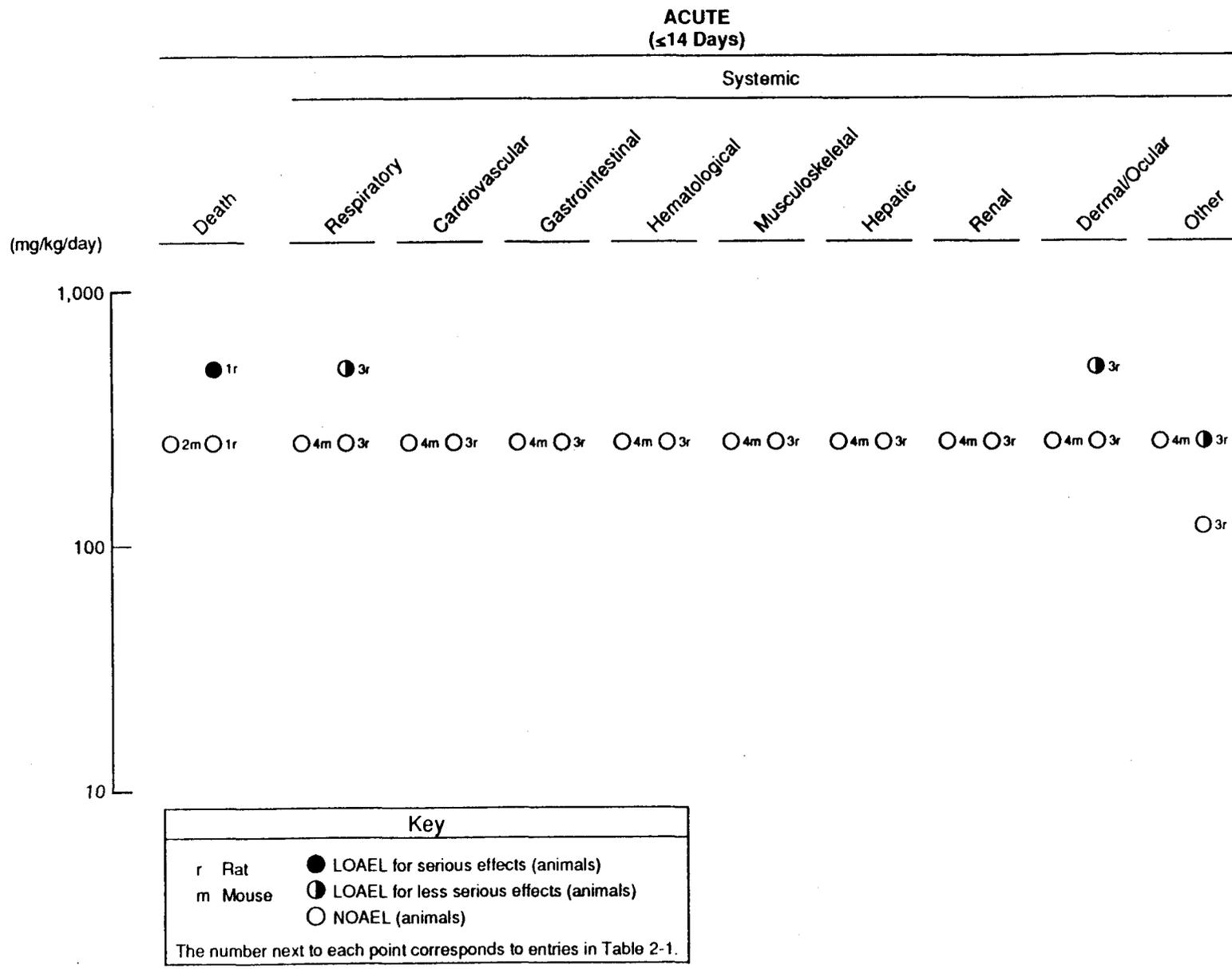


FIGURE 2-1 (Continued)

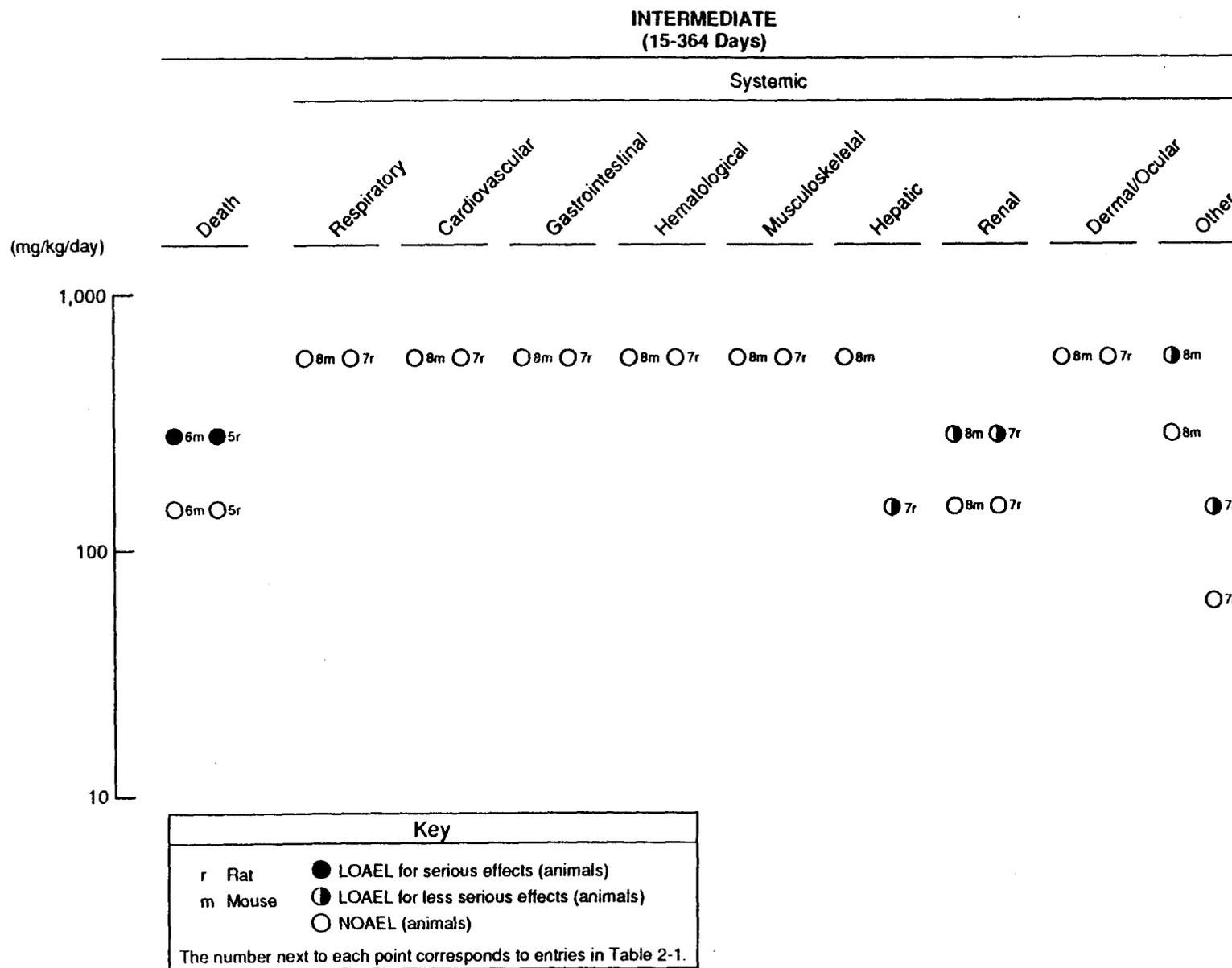
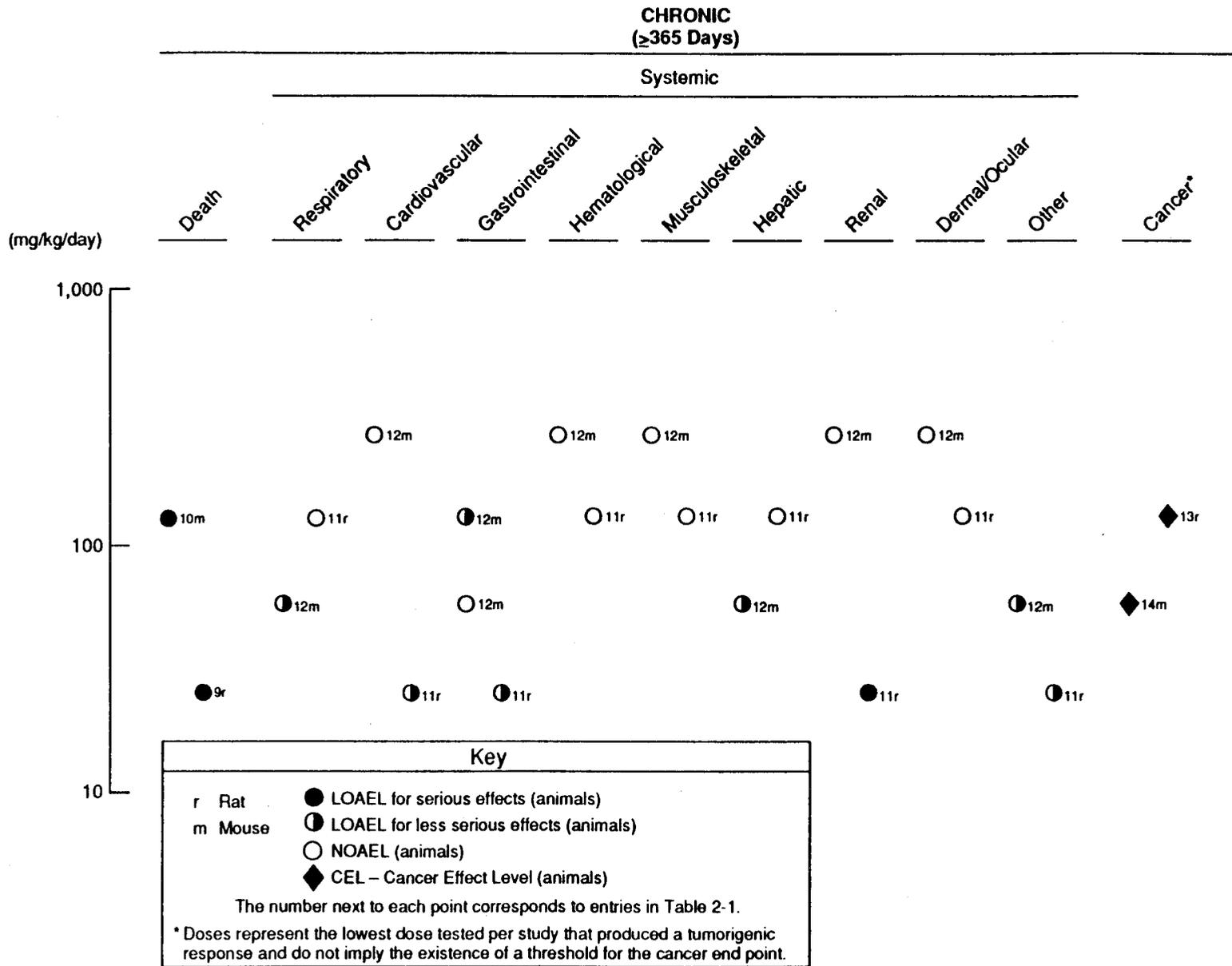


FIGURE 2-1 (Continued)



2. HEALTH EFFECTS

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. HEALTH EFFECTS

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 2-1 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

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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.

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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

2. HEALTH EFFECTS

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.

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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 2-1. 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.

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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.

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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

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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

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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).

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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.

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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 typhimurium, 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: | | | | |
| <u>Salmonella typhimurium</u> (plate incorporation) | Gene mutation | - | - | Weill-Thevenet et al. 1981 |
| <u>S. typhimurium</u> (liquid preincubation) | Gene mutation | - | - | Florin et al. 1980 |
| <u>S. typhimurium</u> (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

2. HEALTH EFFECTS

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. HEALTH 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.

2. HEALTH EFFECTS

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 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 2,3-benzofuran is available. Where adequate information is

2. HEALTH EFFECTS

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).

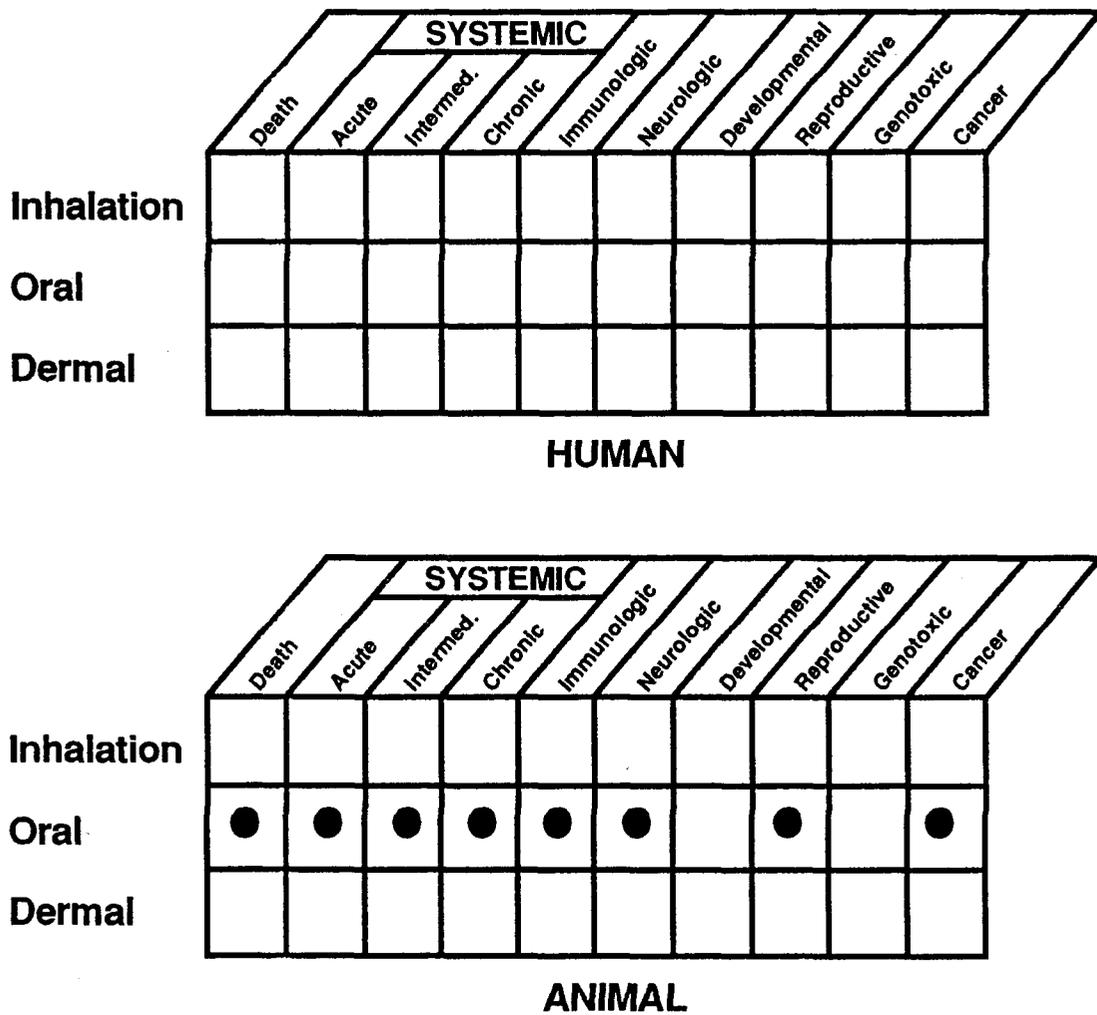
No data exist on the health effects of 2,3-benzofuran in humans. No data exist on the health effects of 2,3-benzofuran in animals following inhalation or dermal exposure. Information on the health effects in rats and mice following oral exposure to 2,3-benzofuran comes primarily from a well-conducted 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

2. HEALTH EFFECTS

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



● Existing Studies

2. HEALTH EFFECTS

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

2. HEALTH EFFECTS

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. typhimurium 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

2. HEALTH EFFECTS

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

2. HEALTH EFFECTS

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.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

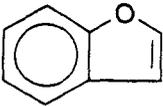
Table 3-1 lists common synonyms, trade names, and other pertinent identification information for 2,3-benzofuran.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of 2,3-benzofuran.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of 2,3-Benzofuran

| Characteristic | Information | Reference |
|-------------------------|--------------------------------------------------------------------------------------|-------------------------------------|
| Chemical name | 2,3-Benzofuran | CLPSD 1990 |
| Synonyms | Benzofuran; cumaron; coumarone; benzo(b)furan; benzofurfuran; 1-oxindene | Windholz et al. 1983 Sax 1984 |
| Trade names | No data | |
| Chemical formula | C ₈ H ₆ O | Weast 1985 |
| Chemical structure |  | Windholz et al. 1983 |
| Identification numbers: | | |
| CAS registry | 271-89-6 | Sax 1984 |
| NIOSH RTECS | DF6423800 | Sax 1984 |
| EPA hazardous waste | No data | |
| OHM/TADS | No data | |
| DOT/UN/NA/IMCO shipping | No data | |
| HSDB | 4173 | NLM 1989 |
| NCI | C56166 | NLM 1989 |

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Physical and Chemical Properties of 2,3-Benzofuran

| Property | Information | Reference |
|--------------------------|--------------------------------------------------------------------------------------------|----------------------|
| Molecular weight | 118.14 | Weast 1985 |
| Color | Colorless | Sax and Lewis 1987 |
| Physical state | Liquid | Sax and Lewis 1987 |
| Melting point | -18°C | Weast 1985 |
| Boiling point | 175°C | Weast 1985 |
| Density at 20°C | 1.0948 | Powers 1980 |
| Odor | Aromatic | Windholz et al. 1983 |
| Odor threshold: | | |
| Water | No data | |
| Air | No data | |
| Solubility: | | |
| Water at 20°C | Insoluble | Windholz et al. 1983 |
| Organic solvents | Miscible with benzene, petroleum ether, absolute alcohol and ether | |
| Partition coefficients: | | |
| Log octanol/water | 2.67 | Leo et al. 1971 |
| Log K_{oc} | No data | |
| Vapor pressure at 20°C | No data | |
| Henry's law constant: | | |
| at 20°C | No data | |
| Autoignition temperature | No data | |
| Flashpoint | No data | |
| Flammability limits | No data | |
| Conversion factors | 1 ppm = 4.83 mg/m ³ (calculated) 1 mg/m ³ = 0.21 ppm (calculated) | |
| Explosive limits | No data | |

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

2,3-Benzofuran is produced as a component of the crude heavy solvent fraction of the coal-tar light oil formed by the coking of bituminous coal (HSDB 1989; Windholz et al. 1983). 2,3-Benzofuran is not isolated for commercial purposes (HSDB 1989). The fraction of this coal-tar oil distilling at 167-184°C contains small quantities (probably less than 10%) (Powers 1980) of 2,3-benzofuran (also known as coumarone) and also indene (approximately 30%) (NTP 1989), indan, substituted benzenes, and related compounds (CFR 1989a). This fraction of coal oil is used to produce a polymer called coumarone-indene resin (Powers 1980). The polymerization is accomplished by addition of an acid catalyst such as boron trifluoride (NTP 1989) or sulfuric acid (HSDB 1989). Coumarone-indene resin hardens when heated and is used to make floor tiles and other products (HSDB 1989; Morris 1953; NTP 1989). Coumarone-indene resin is produced by the Neville Chemical Company of Neville Island, Pennsylvania (SRI 1989).

No quantitative data were located regarding the production of 2,3-benzofuran or coumarone-indene resin, although it is reported that virtually all of the resin-forming fraction produced by destructive distillation of coal is polymerized (Powers 1980). No information was located concerning the stability or decomposition products of coumarone-indene resin.

4.2 IMPORT/EXPORT

Imports of 2,3-benzofuran in 1977 and 1979 have been reported to be 1,840 metric tons and 0.0009 metric tons, respectively (HSDB 1989). Current information regarding 2,3-benzofuran import was not located.

No data were located regarding the export of 2,3-benzofuran.

4.3 USE

2,3-Benzofuran is not isolated for commercial purposes, and no information was located regarding uses of isolated 2,3-benzofuran. However, the coumarone-indene resin may be used as a coating on grapefruit, lemons, limes, oranges, tangelos, and tangerines (CFR 1989a). Coumarone-indene resin is also used in the production of paints and varnishes for corrosion-resistant coatings (Morris 1953; NTP 1989) and water-resistant coatings on paper products and fabrics (NTP 1989) and as adhesives in food containers (CFR 1989d). Coumarone-indene resin has been used in asphalt floor tiles (Morris 1953; Wilson and McCormick 1960).

No data were located which would indicate the extent to which 2,3-benzofuran or coumarone-indene resin is currently used in these products.

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.4 DISPOSAL

2,3-Benzofuran is not listed as a hazardous waste by the EPA. No data were located regarding rules or regulations which control the disposal of 2,3-benzofuran.

No data were located regarding disposal methods or disposed quantities of waste 2,3-benzofuran.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

2,3-Benzofuran is a colorless organic liquid with an aromatic odor. It is produced by the destructive distillation of coal, and may also be formed during processing of fossil fuels, such as coke production and coal gasification. Limited data indicate that 2,3-benzofuran may partition to soils and sediments from water, but the information available is insufficient to predict the environmental fate of this compound. Substantial bioconcentration in aquatic organisms is not expected based on the physical/chemical properties of 2,3-benzofuran.

Monitoring data on 2,3-benzofuran in environmental media are scarce. Potential human exposure to 2,3-benzofuran may occur by ingestion of foods treated with coumarone-indene resin; however, migration of 2,3-benzofuran from this resin has not been confirmed. Occupational exposure to 2,3-benzofuran may occur in several energy-related industries, and individuals living in the vicinity of hazardous waste sites at which this compound has been detected may also be exposed. The EPA has identified 1,177 NPL sites. 2,3-Benzofuran has been found at 5 of the sites evaluated for the presence of this chemical (View 1989). However, it is not known how many of the 1,177 NPL sites have been evaluated for 2,3-benzofuran. As more sites are evaluated by the EPA, the number may change. The frequency of the sites in the United States at which 2,3-benzofuran was found can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

2,3-Benzofuran may be released to the environment from production and use of 2,3-benzofuran-containing products, and from coke production, coal gasification, and oil-shale facilities. 2,3-Benzofuran is not listed on the SARA Section 313 Toxics Release Inventory (TRI).

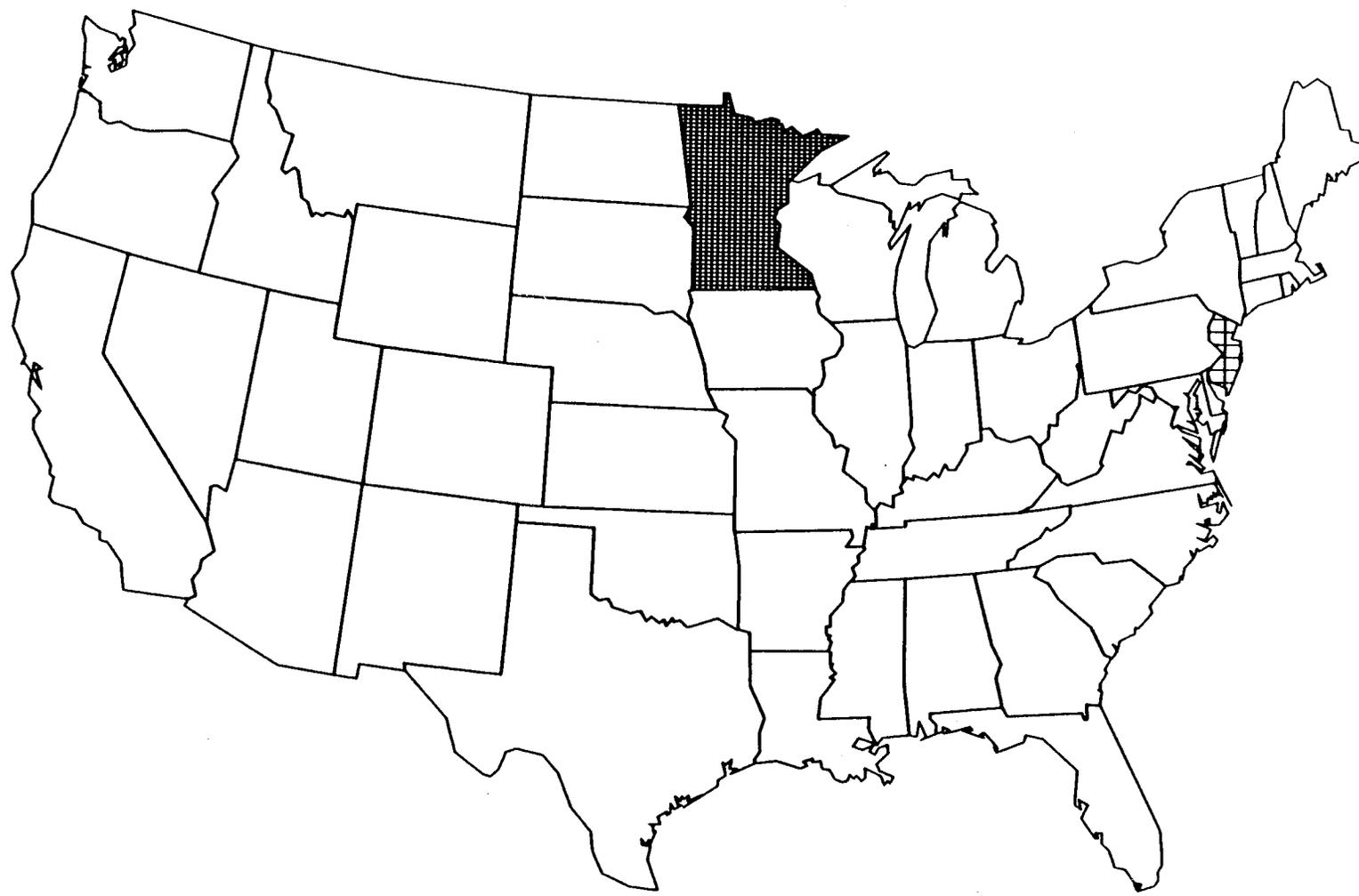
5.2.1 Air

Data on 2,3-benzofuran air emissions are sparse. No information was located regarding 2,3-benzofuran releases from production facilities. However, 2,3-benzofuran was detected in emissions from a Swedish floor finish used on domestic flooring (van Netten et al. 1988), and in emissions from the pyrolysis of silk (Junk and Ford 1980), and in combustor flue gas emissions from fluidized-bed coal combustion at a concentration of 900 ng/g (Hunt et al. 1982). Exhaust produced by an automobile burning simple hydrocarbon fuels contained 2,3-benzofuran at concentrations ranging from less than 0.1 to 2.8 ppm (Seizinger and Dimitriades 1972), but an analysis of air in a highway tunnel in use by both diesel- and gasoline-powered vehicles indicated no 2,3-benzofuran (Hampton et al. 1982).

5.2.2 Water

2,3-Benzofuran may be released to water from coal gasification facilities. 2,3-Benzofuran was detected in coal gasification facility effluents at concentrations ranging from 6 to 267 ppb, but was not detected

FIGURE 5-1. FREQUENCY OF NPL SITES WITH 2,3-BENZOFURAN CONTAMINATION *



FREQUENCY  2 SITES  3 SITES

* Derived from View 1989

5. POTENTIAL FOR HUMAN EXPOSURE

(detection limit 0.1 ppb) in effluents from oil shale processing facilities (Pellizzari et al. 1979). 2,3-Benzofuran was also detected in 1 of 18 waste water concentrates (Lucas 1984). Data from the Contract Laboratory Program (CLP) Statistical Database indicate that 2,3-benzofuran was found at a concentration of 770 ppb in a groundwater sample, but was not found in any surface water samples, taken at one hazardous waste site (CLPSD 1990). It is not known how many hazardous waste sites have been evaluated for 2,3-benzofuran. Note that these data from the CLP Statistical Database represent frequency of occurrence and concentration information for NPL sites only.

5.2.3 Soil

2,3-Benzofuran was found at a concentration of 60 ppb in one soil/sediment sample taken at one hazardous waste site (CLPSD 1990). It is not known how many hazardous waste sites have been evaluated for 2,3-benzofuran. Note that these data from the CLP Statistical Database represent frequency of occurrence and concentration information for NPL sites only.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

No information was located on the transport and partitioning of 2,3-benzofuran in the atmosphere. Based on the high boiling point of 2,3-benzofuran, volatilization would be expected to be slow, but because the vapor pressure of the chemical is unknown, it is not possible to predict how 2,3-benzofuran will partition in the atmosphere.

2,3-Benzofuran is reported not to be soluble in water (Windholz et al. 1983). However, based on its octanol/water partition coefficient (Table 3-2), the solubility of 2,3-benzofuran may be on the order of 200 mg/L, using the empirical regressions of Hassett et al. (1983) for hydrophobic organic chemicals.

2,3-Benzofuran may partition from water to soils and sediments. The extent of adsorption of neutral organic compounds by soils is often correlated with the organic-carbon content of the soil (Hassett et al. 1983). When adsorption is expressed as a function of organic-carbon content, an organic carbon/water partition coefficient (K_{oc}) is generated, and may be used to classify the relative mobility of the chemical in soil. Based on its octanol/water partition coefficient, an estimated K_{oc} for 2,3-benzofuran is about 330, using the empirical regression of Hassett et al. (1983). This K_{oc} implies that 2,3-benzofuran has a medium mobility in soil, using the mobility classifications of Roy and Griffin (1985), and would be most mobile in soils and groundwater where the organic-carbon content is low. No soil adsorption studies on 2,3-benzofuran were located. A coal-tar/water partition coefficient of 912 for 2,3-benzofuran was derived that was similar in magnitude to the octanol/water partition coefficient (Rostad et al. 1985).

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Lignite coal is able to adsorb 2,3-benzofuran from aqueous solution (Humenick et al. 1982), which indirectly confirms the expectation that the mobility of the chemical will be influenced by the distribution of organic carbon.

The potential for 2,3-benzofuran to be bioconcentrated by aquatic organisms is likely to be moderate. A bioconcentration factor (BCF) is the ratio of the concentration of a chemical in the tissues of aquatic animals to the concentration of the chemical in the water in which they live. No experimentally measured value for the BCF of 2,3-benzofuran was located, but the octanol-water partition coefficient (K_{OW}) of 2,3-benzofuran has been measured as 468 (Leo et al. 1971). The empirical regressions of Neeley et al. (1974) relate the values of K_{OW} , and BCF for other compounds, and can be used to estimate that the BCF of 2,3-benzofuran is approximately 40. If this estimate is correct, substantial bioconcentration of 2,3-benzofuran by aquatic organisms would not be expected.

5.3.2 Transformation and Degradation

5.3.2.1 Air

No information was located on the transformation or degradation of 2,3-benzofuran in the atmosphere.

5.3.2.2 Water

No information was located on the transformation or degradation of 2,3-benzofuran in water.

5.3.2.3 Soil

No information was located on the transformation or degradation of 2,3-benzofuran in soils, sediments, or waste water treatment processes.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

2,3-Benzofuran was detected, but not quantitated, in 1 of 10 samples of ambient air taken in an industrial area in the Kanawha Valley, West Virginia (Erickson and Pellizzari 1978). No other monitoring data for 2,3-benzofuran in the United States were located. However, one study identified 2,3-benzofuran among pollutants in the air of the Southern Black Forest in Germany (Juttner 1986).

5.4.2 Water

No information was located regarding 2,3-benzofuran in surface water in the United States. 2,3-Benzofuran was detected in contaminated groundwater at a coal-tar distillation and wood-preserving facility in Minnesota (Rostad et al. 1985).

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5.4.3 Soil

No studies were located regarding occurrence of 2,3-benzofuran in soils. 2,3-Benzofuran was among those chemicals selected as representative compounds of waste chemicals from energy production for, subsurface transport research (Zachara et al. 1984).

5.4.4 Other Environmental Media

2,3-Benzofuran has not generally been reported in foods. However, 2,3-benzofuran was detected among the volatile constituents of freeze-dried whey powder subjected to accelerated browning (Ferretti and Flanagan 1971). It was also detected in three samples of human milk (Pellizzari et al. 1982) and is reportedly a constituent of cigarette smoke (Curvall et al. 1984; Florin et al. 1980; Schlotzhauer and Chortyk 1987).

Although 2,3-benzofuran is a component of coumarone-indene resin and this resin has been approved by the FDA for use as a coating on citrus fruits, as a component of food-preparation utensils, and as an adhesive in food packages (see Table 7-1), no information was located confirming that coumarone-indene resin is currently used on food in the United States. Furthermore, no data were located to indicate that 2,3-benzofuran migrates from the resin into foodstuffs.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Humans may be exposed to 2,3-benzofuran by inhalation, ingestion, or dermal absorption. Based on the limited data available, exposure of the general population to 2,3-benzofuran does not appear to be substantial. However, since this compound has been detected at hazardous waste sites, is reported to be a component of cigarette smoke, and is one monomer in a resin which may be used as a coating on citrus fruits and in packaging materials for foods, human exposure may be possible from these sources. People in Britain who had died in fires had 2,3-benzofuran in some blood samples, but no source of exposure was identified (Anderson and Harland 1980). 2,3-Benzofuran was detected in human milk (Pellizzari et al. 1982); this indicates possible exposure of the mother and is an exposure source for the infant.

Occupational exposure to 2,3-benzofuran may occur in several energy-related industries. 2,3-Benzofuran is part of the naphtha fraction of coal distillates and exposure is possible in coke production and coal gasification facilities (see Chapter 4). Exposure may also occur during the polymerization process used to produce coumarone-indene resin. 2,3-Benzofuran was not included in the NIOSH National Occupational Hazard Survey or the National Occupational Exposure Survey. However, the naphtha fraction of coal tar is considered in the NIOSH (1978) evaluation of occupational hazards associated with coal gasification.

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5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Individuals occupationally exposed to coal tars or the naphtha fraction of coal-tar distillate have potentially high exposure to 2,3-benzofuran. Persons living near industrial sources or hazardous waste sites contaminated with 2,3-benzofuran may be exposed to 2,3-benzofuran. There are insufficient data to identify any other populations with potentially high exposure to this compound.

5.7 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 2,3-benzofuran is available. Where adequate information is not available, ATSDR, in conjunction with the 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.

5.7.1 Data Needs

Physical and Chemical Properties. Measured values of the physical and chemical properties of 2,3-benzofuran necessary to predict the environmental fate and transport of this chemical are not available. Reliable measurements of the vapor pressure, solubility in water, Henry's law constant, and K_{oc} would be useful for more accurate prediction of the behavior of 2,3-benzofuran in environmental media.

Production, Import/Export, Use, and Disposal. No recent quantitative data were located on the production, import/export, use, or disposal of 2,3-benzofuran. Virtually all of the 2,3-benzofuran produced by the destructive distillation of coal is reportedly used in the production of coumarone-indene resin (Powers 1980), but no information was located detailing the current uses of this resin, the composition of this resin, the amount of 2,3-benzofuran emitted from the resin, or the current production volume of the resin. 2,3-Benzofuran is not listed as a hazardous waste by the EPA; therefore, no regulations restricting land disposal apply to this chemical. Data required to assess potential human exposure to this chemical include the amount of production and import/export of 2,3-benzofuran and coumarone-indene resin, and emission rates of 2,3-benzofuran from the resin. If the data indicate that 2,3-benzofuran is emitted from the resin, then current information on the nature and extent of use of the resin will also be

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necessary. Data on environmental releases of 2,3-benzofuran from production facilities and disposal methods employed for wastes containing this chemical would also be helpful to assess potential human exposure.

Environmental Fate. The available data on partitioning, transport, and transformation are insufficient to predict the environmental fate of 2,3-benzofuran. Measurements of the rate of photodegradation of 2,3-benzofuran in the atmosphere and determination of the composition and fate of the decay products would be useful to predict the atmospheric fate of this compound. Information regarding the potential for 2,3-benzofuran to photodegrade or oxidize in water or to biodegrade in water or soil, and the rates at which these reactions occur, would be useful in predicting the fate of the compound in these media. Physical/chemical properties suggest that 2,3-benzofuran can partition to soils (Hassett et al. 1983; Roy and Griffin 1985). Verification of this prediction by measurements of the adsorption and desorption of 2,3-benzofuran by soils and sediments, and measurement of the rate of volatilization of the compound from water, would be useful in predicting the transport and partitioning of 2,3-benzofuran among environmental media.

Bioavailability from Environmental Media. The available data are insufficient to assess the bioavailability of 2,3-benzofuran from environmental media. In vitro evidence suggests that 2,3-benzofuran would be less available from organic-rich particles than from organic-poor particles (Sehnert and Risby 1988), but confirmation of this prediction with in vivo studies would be useful. Animal studies have used gavage in oil for exposure to 2,3-benzofuran (NTP 1989) but no quantitative information concerning absorption is available. Additional information on the bioavailability of 2,3-benzofuran would be useful to assess the extent of absorption of 2,3-benzofuran from environmental media.

Food Chain Bioaccumulation. No data were located regarding the bioconcentration of 2,3-benzofuran in plants, aquatic organisms, or animals. Based on physical/chemical properties, substantial bioconcentration of 2,3-benzofuran is not expected (Leo et al. 1971; Neeley et al. 1974). No data on biomagnification in terrestrial or aquatic food chains are available. Data on bioconcentration of this compound in aquatic species would be useful in confirming the predicted low bioconcentration potential of this compound.

Exposure Levels in Environmental Media. Monitoring data for 2,3-benzofuran are sparse and are insufficient to assess the potential for human exposure to this compound, so no estimates of human intake of this substance are available. Since 2,3-benzofuran is a coal-tar product (Powers 1980), monitoring data for this compound in all environmental media in the vicinity of fossil fuel facilities would help to determine the potential for both general population and occupational exposure. In addition, monitoring foods which come in contact with coumarone-indene resin for 2,3-benzofuran would be useful to assess the potential for human exposure from food.

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Remedial investigations and feasibility studies at hazardous waste sites are potential sources of information on possible exposures of populations surrounding hazardous waste sites.

Exposure Levels in Humans. 2,3-Benzofuran has been detected in several samples of breast milk (Pellizzari et al. 1982). It is unknown whether the presence of this compound in milk is a result of exposure to 2,3-benzofuran itself, or whether it is a metabolite of other compounds. Biological monitoring of workers in coal gasification or related facilities and of c populations surrounding hazardous waste sites would be useful to evaluate human exposure to this compound.

Exposure Registries. No exposure registries for 2,3-benzofuran were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

No information was located on any on-going studies on the fate, transport, or potential for human exposure to 2,3-benzofuran. Remedial investigations and feasibility studies at hazardous waste sites may provide information on environmental levels, transport, and transformation of 2,3-benzofuran.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring 2,3-benzofuran in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify 2,3-benzofuran. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. No methods approved by federal agencies or other groups specifically for detection of 2,3-benzofuran were located.

Environmental media or biological samples which contain 2,3-benzofuran are also likely to contain numerous other organic compounds with similar chemical and physical properties. Analysis of such samples generally proceeds by first extracting or concentrating some subset of the organic compounds and then separating and identifying them. Techniques for extraction of organic compounds from environmental media or biological samples include absorption onto a polymer and extraction with an organic solvent. Recovery is generally not complete, and so accurate quantification requires using matrix spikes (EPA 1986c). This has not been done in any studies for 2,3-benzofuran. Sensitive and selective techniques for identification of organic compounds in extracts are well established, using high-resolution gas chromatography (HRGC) to separate the compounds and mass spectrometry (MS) to identify them. HRGC achieves higher resolution than standard gas chromatography (GC) by using wall-coated capillary columns rather than packed columns for separation of compounds. Flame ionization detection is not specific enough for the analysis of 2,3-benzofuran in samples containing numerous other compounds, although it has been used to monitor the stability of 2,3-benzofuran in oil for animal feeding studies (NTP 1989). Accurate quantification of the concentration of chemicals in extracts can be achieved with GC/MS by daily calibration using actual and surrogate standards (EPA 1986c), although this has not been done specifically for 2,3-benzofuran.

6.1 BIOLOGICAL MATERIALS

2,3-Benzofuran has been detected, but not quantified, in samples of blood (Anderson and Harland 1980) and breast milk (Pellizzari et al. 1982). In both cases, volatile and semi-volatile organic compounds were purged from the biological fluids by bubbling with an inert gas at an elevated temperature. The compounds were trapped by adsorption onto a Tenax® cartridge. The percent recovery of 2,3-benzofuran by this purge-and-trap collection method was not examined. The Tenax® cartridge was heated to desorb the organic compounds directly into the inlet of the HRGC equipment. Mass spectrometry was used to identify the compounds, including 2,3-benzofuran, by mass fragmentation patterns. The percent recovery or concentration was not quantified in either study (Anderson and Harland 1980; Pellizzari et al. 1982).

Methods for detection of 2,3-benzofuran in biological materials are summarized in Table 6-1.

TABLE 6-1. Analytical Methods for Determining 2,3-Benzofuran in Biological Materials

| Sample matrix | Preparation method | Analytical method | Sample detection limit | Percent recovery | Reference |
|---------------|------------------------------------------------------------------|-------------------|------------------------|------------------|---------------------------|
| Blood | Nitrogen purging at 95°C, sorption on Tenax®, thermal desorption | HRGC/MS | No data | No data | Anderson and Harland 1980 |
| Breast milk | Helium purging, sorption on Tenax®, thermal desorption | HRGC/MS | No data | No data | Pellizzari et al. 1982 |

HRGC = high-resolution gas chromatography; MS = mass spectrometry

6. ANALYTICAL METHODS

6.2 ENVIRONMENTAL SAMPLES

2,3-Benzofuran can be trapped and concentrated from air samples by passing a large volume of air through a Tenax® (Erikson and Pellizzari 1978; Juttner 1986; van Netten et al. 1988) or Chromosorb (Seizinger and Dimitriades 1972) cartridge. The cartridge is then thermally desorbed into an HRGC/MS detection system similar to that used for biological samples. 2,3-Benzofuran can be concentrated from water samples using the purge-and-trap method (Pellizzari et al. 1979), or extraction with dichloromethane (Rostad et al. 1985), and analyzed by HRGC/MS. 2,3-Benzofuran can be extracted from particulate samples with dichloromethane and analyzed by HRGC/MS (Ferretti and Flanagan 1971; Hunt et al. 1982). The percent recovery of 2,3-benzofuran by these extraction methods has not been analyzed. The amount of 2,3-benzofuran in some environmental samples has been quantified (Pellizzari et al. 1979; Seizinger and Dimitriades 1972), but the precision of the quantification was not examined.

Methods for the determination of 2,3-benzofuran in environmental samples are summarized in Table 6-2.

6.3 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 2,3-benzofuran is available. Where adequate information is not available, ATSDR, in conjunction with the 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.

6.3.1 Data Needs

Methods for Determining Biomarkers of Exposure and Effect. The only known biomarker of exposure to 2,3-benzofuran is its presence in blood (Anderson and Harland 1980) or breast milk (Pellizzari et al. 1982). 2,3-Benzofuran was not found in all samples of blood or breast milk tested, but since existing methods for detection of 2,3-benzofuran in biological samples are not quantitative, it is not possible to assess whether those samples contained no 2,3-benzofuran or whether the method used was not sufficiently sensitive to measure background levels in the population. The levels at which human health effects occur are not known. Only the administered doses, not the target organ concentrations, are known for

TABLE 6-2. Analytical Methods for Determining 2,3-Benzofuran in Environmental Samples

| Sample matrix | Preparation method | Analytical method | Sample detection limit | Percent recovery | Reference |
|--------------------------------------------------------|---------------------------------------------------------------------|-------------------|------------------------|------------------|--------------------------------|
| Forest air | Sorption on Tenax [®] , thermal desorption | HRGC/MS | No data | No data | Juttner 1986 |
| Ambient air | Sorption on Tenax [®] , thermal desorption | HRGC/MS | No data | No data | Erikson and Pellizzari 1978 |
| Indoor air | Sorption on Tenax [®] , thermal desorption | HRGC/MS | No data | No data | van Netten et al. 1988 |
| Automobile exhaust | Sorption on Chromosorb, thermal desorption | HRGC/MS | 0.1 ppm | No data | Seizinger and Dimitriades 1972 |
| Groundwater | Extraction with dichloromethane | HRGC/MS | No data | No data | Rostad et al. 1985 |
| Groundwater and process water | Helium purging, sorption on Tenax [®] , thermal desorption | HRGC/MS | 0.1 ppb | No data | Pellizzari et al. 1979 |
| Whey powder | Extraction with dichloromethane, vacuum distillation | GC/MS | No data | No data | Ferretti and Flanagan 1971 |
| Baghouse filter ash from fluidized-bed coal combustion | Extraction with dichloromethane | HRGC/MS | No data | No data | Hunt et al. 1982 |

GC = gas chromatography; HRGC = high-resolution gas chromatography; MS = mass spectrometry

6. ANALYTICAL METHODS

biological effects occurring in animals (NTP 1989), but these doses are relatively high (30 mg/kg/day or greater, see Chapter 2). Based on the general sensitivity of HRGC/MS methods, it is likely that levels of 2,3-benzofuran at which biological effects occur should be achievable with routine quantification procedures. The overall techniques of extraction followed by HRGC/MS analysis can be made precise, accurate, reliable, and specific, so that the opportunity exists to develop methods for sensitive quantitation of 2,3-benzofuran in biological samples. Refinement of existing purge-and-trap extraction techniques and investigation of alternative concentration techniques such as cryotrapping (Pankow and Rosen 1988) and supercritical fluid extraction (King 1989) would be useful. High-performance liquid chromatography as an alternative to HRGC and Fourier transform infrared spectroscopy and photodiode array detectors as alternatives to MS detection might offer advantages. Investigation of possible metabolites of 2,3-benzofuran as biomarkers of exposure would be most useful if accompanied by development of methods for their detection, such as immunoassay techniques and ³²P post-labelling for identifying macromolecular adducts.

No known biomarkers of effect were located in the literature. Investigation of biomarkers of effect of 2,3-benzofuran would be most useful if it were also to focus on developing precise, accurate, reliable, and specific methods for measuring background levels of the biomarker of effect in the population and also levels at which adverse effects occur.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. The purpose of the analytical methods for 2,3-benzofuran is to identify contaminated areas and to determine if contaminant levels constitute a concern for human health. The media of most concern for human exposure to 2,3-benzofuran are drinking water, soil, and air. It is likely that 2,3-benzofuran exists in these media primarily adsorbed to organic-rich particulates (Hasset et al. 1983). 2,3-Benzofuran has been found relatively infrequently in environmental media, but most samples have excluded particulates. Insufficient work has been done on quantification of 2,3-benzofuran, particularly percent recovery, to determine whether the methods are sensitive enough to measure background levels in the environment (Erikson and Pellizzari 1978; Hunt et al. 1982; Juttner 1986; Pellizzari et al. 1979; Rostad et al. 1985; Seizinger and Dimitriades 1972). The levels of 2,3-benzofuran at which health effects occur in animals are equivalent to 400 ppm in the diet or more (NTP 1989). Existing methods have nominal detection limits of 0.1 ppb (Pellizzari et al. 1979; Seizinger and Dimitriades 1972), indicating that existing methods are probably sensitive enough to detect levels at which health effects occur. The basic techniques of HRGC/MS have the potential for excellent precision, accuracy, reliability, and specificity, with sufficient research and development. One novel technique which may be suitable for in situ monitoring of 2,3-benzofuran in water is surface-enhanced Raman spectroscopy using silver electrodes (Carrabba et al. 1987). No information is available concerning degradation products of 2,3-benzofuran; investigation of 2,3-benzofuran degradation would be most useful if it included development of reliable analytical methods.

6. ANALYTICAL METHODS

6.3.2 On-going Studies

No information was located concerning studies directed towards improving methods for detection of 2,3-benzofuran specifically.

7. REGULATIONS AND ADVISORIES

No regulations or advisories that apply specifically to 2,3-benzofuran were located. 2,3-Benzofuran is one component of coumarone-indene resin and a number of regulations and guidelines have been established for coumarone-indene resin by various national agencies. These values are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to 2,3-Benzofuran*

| Agency | Description | Information | References |
|-----------------|-----------------------------------------------------------------------------------------------------------|-------------|--------------------------------|
| <u>NATIONAL</u> | | | |
| Regulations: | | | |
| a. Food: | | | |
| FDA | Coumarone-indene resin as a protective coating on citrus fruit-maximum residue | 200 ppm | CFR 1989a (21 CFR 172.215) |
| | Coumarone-indene resin as a component of adhesives approved for use in food packaging | Yes | CFR 1989c (21 CFR 175.105) |
| | Coumarone-indene resin as a plasticizer in rubber articles intended for repeated use in contact with food | Yes | CFR 1989d (21 CFR 177.2600) |
| EPA OPP | Exemption from tolerance Coumarone-indene resin used as coating on citrus fruit | Yes | CFR 1989e (40 CFR 180.1001) |

EPA = Environmental Protection Agency; FDA = Food and Drug Administration; OPP = Office of Pesticide Products

*There are no regulations or advisories specifically applicable to 2,3-benzofuran. Because 2,3-benzofuran is one component of coumarone-indene resin, the regulations applicable to Coumarone-indene resin are presented in this table.

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves- as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

9. GLOSSARY

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration_(Lo) (LC_{Lo}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose_(Lo) (LD_{Lo}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

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No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1^* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu\text{g/L}$ for water, mg/kg/day for food, and $\mu\text{g/m}^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

9. GLOSSARY

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD₅₀) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A**USER'S GUIDE****Chapter 1****Public Health Statement**

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2**Tables and Figures for Levels of Significant Exposure (LSE)**

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND**See LSE Table 2-1**

- (1). Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist,

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three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

- (2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.
- (3). Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.
- (4). Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-1).
- (5). Species The test species, whether animal or human, are identified in this column.
- (6). Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.
- (7). System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.
- (8). NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "c").
- (9). LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with

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increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

- (10). Reference The complete reference citation is given in Chapter 8 of the profile.
- (11). CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs-for cancer, but the text may report doses which did not cause a measurable increase in cancer.
- (12). Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND**See LSE Figure 2-1**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure levels for particular exposure duration.

- (13). Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14). Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.
- (15). Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m³ or ppm and oral exposure is reported in mg/kg/day.
- (16). NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17). CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

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- (18). Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1^*).
- (19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation

| Key to figure ^a | Species | Exposure frequency/ duration | System | NOAEL (ppm) | LOAEL (effect) | | Reference |
|----------------------------------|------------|---------------------------------|------------|----------------|--------------------|-----------------------------------------|-------------------------|
| | | | | | Less serious (ppm) | Serious (ppm) | |
| 2 → INTERMEDIATE EXPOSURE | | | | | | | |
| 3 → Systemic | 5 ↓ | 6 ↓ | 7 ↓ | 8 ↓ | 9 ↓ | | 10 ↓ |
| 4 → 18 | Rat | 13 wk 5d/wk 6hr/d | Resp | 3 ^b | 10 (hyperplasia) | | Nitschke et al. 1981 |
| ----- | | | | | | | |
| CHRONIC EXPOSURE | | | | | | | |
| Cancer | | | | | | | 11 ↓ |
| 38 | Rat | 18 mo 5d/wk 7hr/d | | | | 20 (CEL, multiple organs) | Wong et al. 1982 |
| 39 | Rat | 89-104 wk 5d/wk 6hr/d | | | | 10 (CEL, lung tumors, nasal tumors) | NTP 1982 |
| 40 | Mouse | 79-103 wk 5d/wk 6hr/d | | | | 10 (CEL, lung tumors, hemangiosarcomas) | NTP 1982 |

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

12 → ^b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

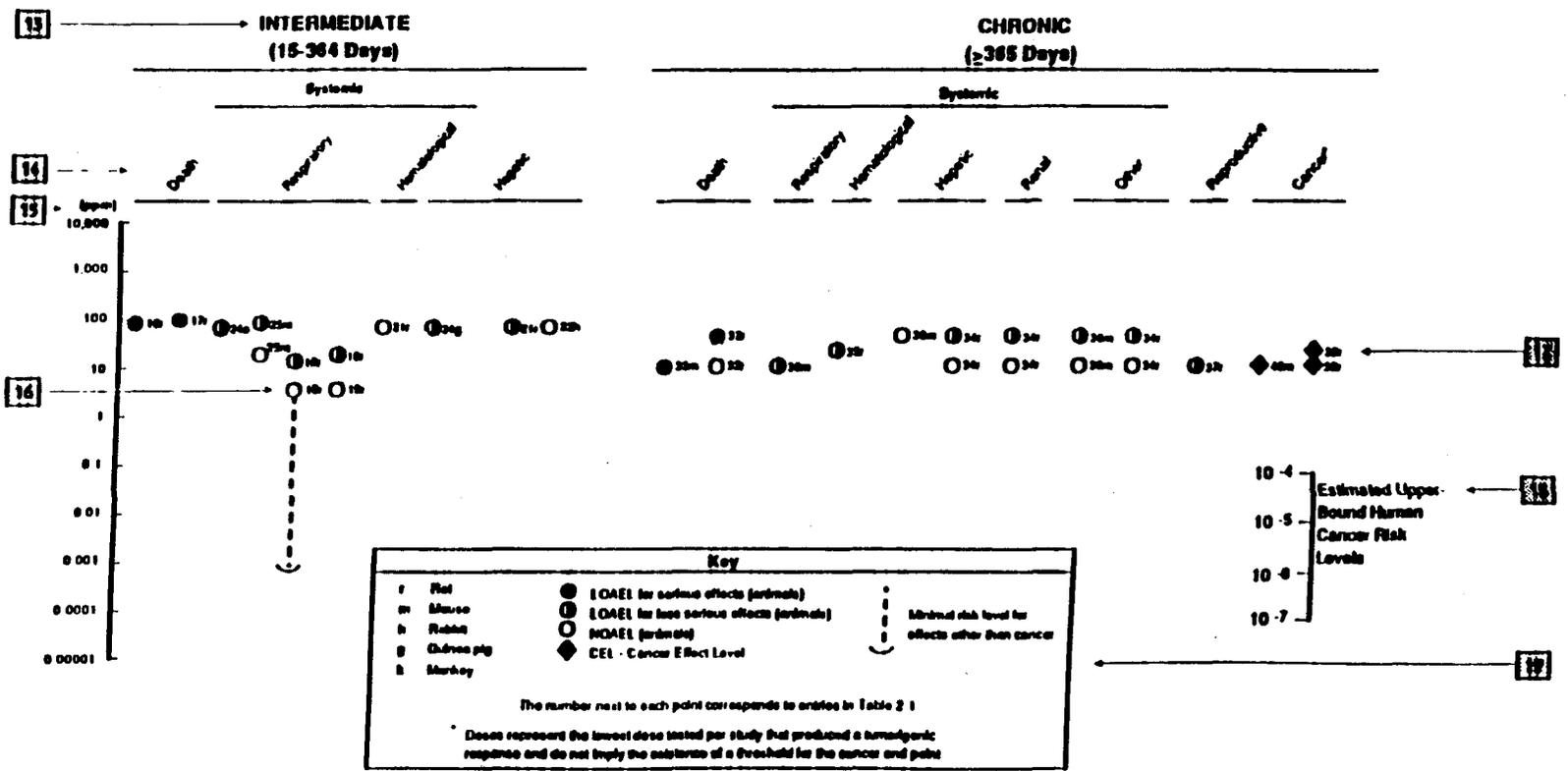


FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

APPENDIX A

Chapter 2 (Section 2.4)**Relevance to Public Health**

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, -chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

APPENDIX A

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continuous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

| | |
|------------------|-----------------------------------------------------------------------|
| ACGIH | American Conference of Governmental Industrial Hygienists |
| ADME | Absorption, Distribution, Metabolism, and Excretion |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| BCF | bioconcentration factor |
| BSC | Board of Scientific Counselors |
| CDC | Centers for Disease Control |
| CEL | Cancer Effect Level |
| CERCL | Comprehensive Environmental Response, Compensation, and Liability Act |
| CFR | Code of Federal Regulations |
| CLP | Contract Laboratory Program |
| cm | centimeter |
| CNS | central nervous system |
| DHEW | Department of Health, Education, and Welfare |
| DHHS | Department of Health and Human Services |
| DOL | Department of Labor |
| ECG | electrocardiogram |
| EEG | electroencephalogram |
| EPA | Environmental Protection Agency |
| EKG | see ECG |
| FAO | Food and Agricultural Organization of the United Nations |
| FEMA | Federal Emergency Management Agency |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| f ₁ | first generation |
| fpm | feet per minute |
| ft | foot |
| FR | Federal Register |
| g | gram |
| GC | gas chromatography |
| HPLC | high performance liquid chromatography |
| hr | hour |
| IDLH | Immediately Dangerous to Life and Health |
| IARC | International Agency for Research on Cancer |
| ILO | International Labor Organization |
| in | inch |
| K _d | adsorption ratio |
| kg | kilogram |
| K _{oc} | octanol-soil partition coefficient |
| K _{ow} | octanol-water partition coefficient |
| L | liter |
| LC | liquid chromatography |
| LC _{Lo} | lethal concentration low |
| LC ₅₀ | lethal concentration 50 percent kill |
| LD _{Lo} | lethal dose low |
| LD ₅₀ | lethal dose 50 percent kill |
| LOAEL | lowest-observed-adverse-effect level |
| LSE | Levels of Significant Exposure |
| m | meter |
| mg | milligram |

APPENDIX B

| | |
|----------|-------------------------------------------------------|
| min | minute |
| mL | milliliter |
| mm | millimeters |
| mmol | millimole |
| mppcf | millions of particles per cubic foot |
| MRL | Minimal Risk Level |
| MS | mass spectroscopy |
| NIEHS | National Institute of Environmental Health Sciences |
| NIOSH | National Institute for Occupational Safety and Health |
| NIOSHTIC | NIOSH's Computerized Information Retrieval System |
| nm | nanometer |
| ng | nanogram |
| NHANES | National Health and Nutrition Examination Survey |
| nmol | nanomole |
| NOAEL | no-observed-adverse-effect level |
| NOES | National Occupational Exposure Survey |
| NOHS | National Occupational Hazard Survey |
| NPL | National Priorities List |
| NRC | National Research Council |
| NTIS | National Technical Information Service |
| NTP | National Toxicology Program |
| OSHA | Occupational Safety and Health Administration |
| PEL | permissible exposure limit |
| pg | picogram |
| pmol | picomole |
| PHS | Public Health Service |
| PMR | proportional mortality ratio |
| ppb | parts per billion |
| ppm | parts per million |
| ppt | parts per trillion |
| REL | recommended exposure limit |
| RfD | Reference Dose |
| RTECS | Registry of Toxic Effects of Chemical Substances |
| sec | second |
| SCE | sister chromatid exchange |
| SIC | Standard Industrial Classification |
| SMR | standard mortality ratio |
| STEL | short-term exposure limit |
| STORET | <u>STORAGE</u> and <u>RETRIEVAL</u> |
| TLV | threshold limit value |
| TSCA | Toxic Substances Control Act |
| TRI | Toxic Release Inventory |
| TWA | time-weighted average |
| U.S. | United States |
| UF | uncertainty factor |
| WHO | World Health Organization |
| > | greater than |
| ≥ | greater than or equal to |
| = | equal to |

APPENDIX B

| | |
|----|-----------------------|
| < | less than |
| ≤ | less than or equal to |
| % | percent |
| α | alpha |
| β | beta |
| δ | delta |
| γ | gamma |
| μm | micron |
| μg | microgram |

APPENDIX C

PEER REVIEW

A peer review panel was assembled for 2,3-benzofuran. The panel consisted of the following members: Dr. David Warshawsky, Associate Professor, Environmental Health, University of Cincinnati; Dr. Raymond Smith, Instructor, Department of Pathology and Microbiology, University of Nebraska; and Dr. Anthony DeCaprio, Consultant, Albany, New York. These experts collectively have knowledge of 2,3-benzofuran's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. A second panel of reviewers was assembled to review the sections on mitigation of effects. This panel consisted of: Dr. Brent Burton, Medical Director, Oregon Poison Center, Oregon Health Sciences University, Portland, Oregon; Dr. Alan Hall, Private Consultant, Evergreen, Colorado; and Dr. Alan Woolf, Director of Clinical Pharmacology and Toxicology, Massachusetts Poison Control System, The Children's Hospital, Boston, Massachusetts. All reviewers were selected in conformity with the conditions for peer review specified in the Comprehensive Environmental Response, Compensation, and Liability Act of 1986, Section 104.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.