TOXICOLOGICAL PROFILE FOR 2-BUTANONE

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

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DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

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.

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about 2-butanone(methyl ethyl ketone) 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-butanone has been found at 137 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for 2-butanone. As EPA evaluates more sites, the number of sites at which 2-butanone is found may change. The information is important for you because 2-butanone may cause harmful health effects and because these sites are potential or actual sources of human exposure to 2-butanone.

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 are 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 substance such as 2-butanone, 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-BUTANONE?

2-Butanone, also known as methyl ethyl ketone (MEK), is a colorless liquid with a sweet, but sharp odor. 2-Butanone is manufactured in large amounts for use in paints, glues, and other finishes because it rapidly evaporates and will dissolve many substances, It will quickly evaporate into the air. 2-Butanone is often found dissolved in water or as a gas in the air. 2-Butanone is also a natural product made by some trees and is found in some fruits and vegetables. The exhausts of cars and trucks release 2-butanone into the air. 2-Butanone is usually found in the air, water, and soil of landfills and hazardous waste sites.

In water, 2-butanone can be changed to a more simple chemical form by natural biological processes and will be broken down in about 2 weeks. It will not be deposited in the sediment of rivers or lakes, and it is not expected to concentrate in fish. In air, 2-butanone will break down under the influence of sunlight, although it does not react with sunlight directly. One-half of any given amount of 2-butanone in the air will break down in 1 day or less. It is not known if 2-butanone changes to a more simple form by

natural biological processes in soil, but it is expected to do so because similar substances are broken down by these processes. 2-Butanone will not stick to soil, and if it is spilled onto soil, it will travel through the soil into underground water sources. Some of the 2-butanone found in soil or water will also evaporate to the air.

You will find more information on the chemical properties of 2-butanone in Chapter 3. The uses of 2-butanone are given in Chapter 4. More information on how 2-butanone behaves in the environment is found in Chapter 5.

1.2 HOW MIGHT I BE EXPOSED TO 2-BUTANONE?

2-Butanone can enter the environment in a number of different ways. It can enter the air or water from the waste of manufacturing plants. 2-Butanone is present in many different types of paints and glues used both in the home and in industry. As these products dry, 2-butanone will enter the air. 2-Butanone is also in air because it is released in the exhaust of cars and trucks. Some trees in the forest release 2-butanone to the air.

We do not know the background levels of 2-butanone in air, water, or soil. We know that 2-butanone is found naturally in some foods. We know it is found at hazardous waste sites, and it is also found occasionally in drinking water and often in the air of cities. You may also be exposed to 2-butanone by smoking cigarettes.

You may be exposed to higher levels of 2-butanone if you use glues of coatings containing it in a small enclosed area that does not have good air flow, People who use it at work have a good chance of being exposed to 2-butanone. 2-butanone is used in such industries as shoes factories, printing plants, plastics factories, and sporting goods manufacturers. People who live near a toxic waste site where 2-butanone is kept may breathe it if it evaporates into the air, or drink it if it gets into the water supply, especially when the water supply comes from wells.

You can find more information on how much 2-butanone is in the environment and how you can be exposed to it in Chapter 5.

1.3 HOW CAN 2-BUTANONE ENTER AND LEAVE MY BODY?

2-butanone can enter your body if you breathe air that contains it, through your skin if it touches you, or through your mouth if you eat food or drink water that has 2-butanone in it. Studies have shown that, if there is 2-butanone in the air you breathe, at least half of what you breathe in will enter your body. The other half will leave in the air you breathe out. We do not know how much 2-butanone will stay in your body if you drink it or if it touches your skin. The amount of 2-butanone that actually enters your body depends on how much is in the air you breathe, how much is in your food or

water, or how much gets on your skin. The amount of 2-butanone that enters your body also depends on how long you breathe it or how long it is on your skin before you wash it off. Your body gets rid of 2-butanone in urine and in the air you breathe out. 2-Butanone is not a chemical that stays in your body for very long; it will be gone by the next day. For more information on how 2-butanone gets into and leaves your body, see Chapter 2.

1.4 HOW CAN 2-BUTANONE AFFECT MY HEALTH?

Some people who breathed air that contained 2-butanone first noticed its sweet, sharp odor at a concentration of 5-8 parts of 2-butanone per million parts of air (5-8 ppm). The main health effects that have been seen in humans who breathed higher concentrations of 2-butanone are mild irritation of the nose, throat, eyes, and skin.

Serious health effects in animals have been seen only at very high concentrations of 2-butanone. These high concentrations are not expected in the usual use of 2-butanone or in the vicinity of hazardous waste sites. Studies in animals have shown that 2-butanone does not cause serious damage to the nervous system or the liver, but mice that breathed low levels for a short time had temporary behavioral effects. 2-Butanone alone does not have serious effects on the liver or nervous system, but it can cause other chemicals to become more harmful to these systems.

Guinea pigs, rats, and mice that breathed high levels of 2-butanone for a short time became unconscious and died. Pregnant rats and mice that breathed air containing high levels of 2-butanone had underdeveloped fetuses. The rats that swallowed very high concentrations of 2-butanone in water also developed signs of nervous system effects such as inactivity, drooping eye lids, and uncoordinated muscle movement. Some rats and mice that swallowed water containing high concentrations of 2-butanone died. Rats that received water containing a lower concentration of 2-butanone had mild kidney damage. Skin irritation developed in rabbits and guinea pigs that had small amounts of 2-butanone dropped on their skin. Rabbits that had small amounts of 2-butanone dropped in their eyes had serious eye irritation. We do not know whether 2-butanone causes birth defects or affects reproduction in humans. Reproductive effects were not seen in animals exposed to 2-butanone. We have no information about whether 2-butanone causes cancer in humans or animals.

A more complete discussion of the health effects of 2-butanone 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-BUTANONE?

No specific medical test is available to determine whether you have been exposed to 2-butanone. Studies in humans and animals have shown that it is possible to detect 2-butanone or its breakdown products in the blood, breath,

and urine. The levels of 2-butanone found in the blood, breath, and urine are usually associated with the levels of exposure found in the workplace, but this is more useful for determining exposure of groups of people rather than individuals. Tests for 2-butanone in blood, urine, or breath are useful only for recent exposure because 2-butanone and its breakdown products leave the body rapidly. These considerations are discussed in more detail in Chapters 2 and 6.

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

The Occupational Safety and Health Administration (OSHA) has set an occupational exposure limit of 200 ppm of 2-butanone in the air. The National Institute for Occupational Safety and Health (NIOSH) has also recommended 200 ppm of 2-butanone as the limit for up to a 10-hour work shift in a 40-hour workweek. Because of its odor, you can smell 2-butanone before it harms you. Further information on governmental recommendations 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-butanone (methyl ethyl ketone) 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-butanone based on toxicological studies and epidemiological investigations.

2-Butanone alone is a relatively safe chemical widely used as a insolvent industry. For some uses, 2-butanone is combined with other chemicals thathave serious neurotoxic and hepatotoxic effects. Clinical reports and animal studies have clearly shown that exposure to 2-butanone alone causes minimal chronic neurological or hepatic deficits, if any. It does potentiate both the neurotoxicity of n-hexane and methyl-n-butyl ketone and the hepatotoxicity of carbon tetrachloride and chloroform. The potentiation of neurotoxicity and hepatotoxicity by 2-butanone is discussed in Section 2.6 (Interactions with other Chemicals).

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.

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

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989a), 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

2.2.1.1 Death

No studies were located regarding death of humans following inhalation exposure to 2-butanone.

Acute (4-hour) exposure to 2,000 ppm 2-butanone caused the death of up to 4 of 6 rats within a 14-day observation period after exposure (Carpenter et al. 1949). The cause of death was not reported, but gross necropsy and histopathology confirmed that extraneous infections were not involved. In contrast, exposure of 6 rats to 8,000 ppm 2-butanone for 8 hours resulted in the death of half of the rats (Smyth et al. 1962). Furthermore, the 4-hour LC_{50} in rats, calculated from the dose-response curve, was 11,700 ppm (LaBelle and Brieger 1955). The LC_{50} was determined using similar rats and the same exposure methods used by Carpenter et al. (1949). Mice exposed to a saturated vapor of 2-butanone (estimated concentration: 103,000 ppm) showed a mean survival time of 43 minutes (LaBelle and Brieger 1955). The LT_{50} and LT_{50} in rats exposed to 92,239 ppm 2-butanone were 3 and 0.5 hours, respectively (Klimisch 1988). The LT_{50} represents the time of exposure after which 50% of the animals died within 14 days following exposure. The LT_0 represents the time of exposure after which no animals died within 14 days following exposure. No deaths were reported after a 4-hour exposure of mice to 2,438 ppm 2-butanone (De Ceaurriz et al. 1983). Death of guinea pigs occurred within 45 minutes of exposure to 100,000 ppm 2-butanone and within 200 minutes of exposure to 33,000 ppm (Patty et al. 1935). Gasping respiration was observed at concentrations of 33,000 ppm and higher about 10 minutes before the guinea pigs died.

In intermediate duration studies, no deaths occurred during a 90-day exposure of rats to 5,000 ppm or less, 5 days/week for 6 hours/day (Cavenderet al. 1983). In contrast, five of five rats died within 7 weeks of a planned 15-week exposure to 6,000 ppm, 7 days/week, 8 hours/day (Altenkirch et al. 1978a). The cause of death for all rats exposed to 2-butanone in this study was severe bronchopneumonia confirmed pathologically and histologically. In the same study, rats exposed to n-hexane or a combination of n hexane and 2-butanone did not develop bronchopneumonia. A repeat of this study gave the same results, i.e., death within 7 weeks coincident with confirmed bronchopneumonia (Altenkirch et al. 1978b). Saida et al. (1976) reported no deaths or change in clinical signs in rats exposed to 1,125 ppm 2-butanone continuously for 5 months. Similar results were reported by several groups after intermediate exposures ranging from 200 to 800 ppm in rats and guinea pigs, i.e., no deaths and no change in clinical signs (LaBelle and Brieger 1955; Takeuchi et al. 1983; Toftgard et al. 1981). The LC_{50} the highest NOAEL values, and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

The systemic effects of 2-butanone following inhalation exposure are discussed below. No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, hepatic, or renal effects in humans after inhalation exposure to 2-butanone. The highest NOAEL values and all reliable LOAEL values for each systemic effect for each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

Respiratory Effects. 2-Butanone is irritating to respiratory tissues. A clinical case report of three men exposed to 2-butanone fumes while removing paint from an airplane hangar noted mild respiratory symptoms but did not further describe the nature or extent of the symptoms (Berg 1971). Volunteers exposed to 100 ppm 2-butanone complained of slight nose and throat irritation, which became objectionable at 300 ppm (Nelson et al. 1943). The respiratory tract irritation noted in humans at 100 ppm does not imply that humans are more sensitive to the respiratory effects of 2-butanone than other species tested (see Table 2-l). Another possible explanation is that humans *are* better able to communicate the early signs of irritation compared with the other species tested. Nasal resistance was significantly increased in humans upon exposure to the threshold level of 2-butanone; this response reflects a nasopharyngeal reflex (Doty et al. 1988). The odor threshold for 2-butanone falls in the range 5.4-8.25 ppm (Amoore and Hautala 1983; Doty et al. 1988).

At high concentrations, 2-butanone is also irritating to respiratory tissues of animals. Severe upper respiratory tract irritation was found after a few days in rats exposed to 10,000 ppm, 8 hours/day (Altenkirch et al. 1978a). Guinea pigs exposed to 33,000 ppm had gasping respiration after 180 minutes of exposure and died after 200-260 minutes of exposure. Their

TABLE 2-1. Levels of Significant Exposure to 2-Butanone - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	1 d 4 hr/d				11,700 (LC_{50})	LaBelle and Brieger 1955
2	Rat	1 d 8 hr/d				8,000 (3/6 died)	Smyth et al. 1962
3	Rat	1 d 3 hr/d				92,239	Klimisch 1988
4	Gn pig	1 d 3 hr/d		10,000		33,000	Patty et al. 1935
5	Mouse	43 min				103,000	LaBelle and Brieger 1955
Systemic							
6	Human	1 d 5 min/d	Resp		100 (nose/throat irritation)		Nelson et al. 1943
7	Rat	a few d 8 hr/d	Resp		10,000 (respiratory irritation)		Altenkirch et al. 1978a
8	Rat	7 d 8 hr/d	Hepatic	300			Li et al. 1986
9	Gn pig	1 d 13.5 hr/d	Resp Hepatic Renal Derm/oc	10,000 3,300 3,300 3,300	 10,000 (congestion) 10,000 (congestion) 10,000 (eye irritation, lacrimation)	33,000 (gasping and death) 100,000 (corneal opacity and death)	Patty et al. 1935
Neurological							
10	Human	1 d 4 hr/d		200			Dick et al. 1984, 1988, 1989
11	Gn pig	1 d 13.5 hr/d		3,300		10,000 (narcosis, incoordination)	Patty et al. 1935
12	Mouse	1 d 4 hr/d			1,602 (reduced immobility)		De Ceaurriz et al. 1983

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
Developmental							
13	Rat	10 d Gd 6-15 7 hr/d		1,000		3,000 (extra ribs, delayed ossification)	Deacon et al. 1981
14	Mouse	10 d Gd 6-15 7 hr/d		1,000		3,000 (decreased fetal body weight, sternebral anomalies)	Mast et al. 1989
INTERMEDIATE EXPOSURE							
Death							
15	Rat	12 wk 5 d/wk 7 hr/d		235			LaBelle and Brieger 1955
16	Rat	90 d 5 d/wk 6 hr/d		5,000			Cavender et al. 1983
17	Rat	7 wk 7 d/wk 8 hr/d				6,000 (5/5 died)	Altenkirch et al. 1978a, 1978b
18	Gn pig	12 wk 5 d/wk 7 hr/d		235			LaBelle and Brieger 1955
Systemic							
19	Rat	90 d 5 d/wk 6 hr/d	Resp Cardio Gastro Hemato Musc/sk Hepatic Renal Derm/oc Other	5,000 5,000 5,000 5,000 5,000 5,000 5,000 5,000 5,000			Cavender and Casey 1981; Cavender et al. 1983
Immunological							
20	Rat	90 d 5 d/wk 6 hr/d		5,000			Cavender and Casey 1981; Cavender et al. 1983

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
Neurological							
21	Rat	7 wk 7 d/wk 8 hr/d		6,000			Altenkirch et al. 1978a, 1978b
22	Rat	90 d 5 d/wk 6 hr/d		5,000			Cavender and Casey 1981; Cavender et al. 1983
Reproductive							
23	Rat	90 d 5 d/wk 6 hr/d		5,000			Cavender and Casey 1981; Cavender et al. 1983

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

Cardio = cardiovascular; d = day; Derm/oc = dermal/ocular; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration 50% kill; LOAEL = lowest-observed-adverse-effect level; min = minutes; Musc/sk = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

FIGURE 2-1. Levels of Significant Exposure to 2-Butanone - Inhalation

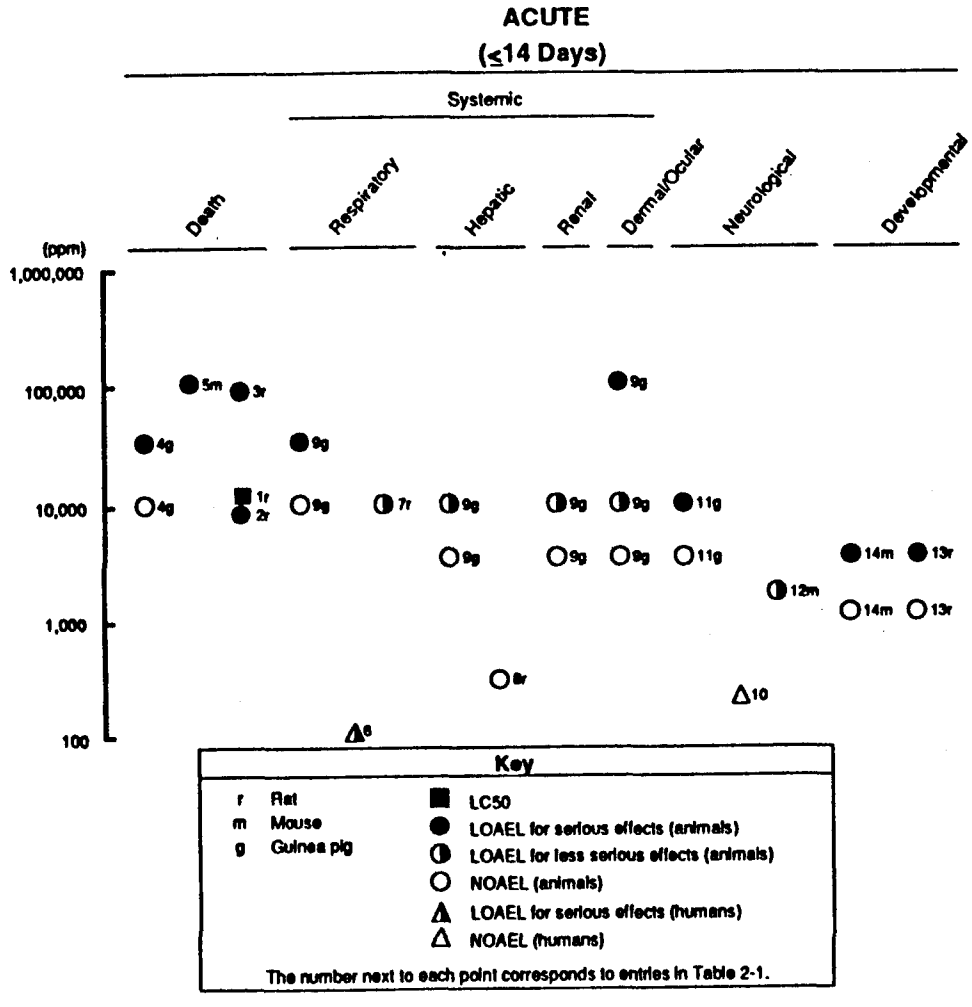
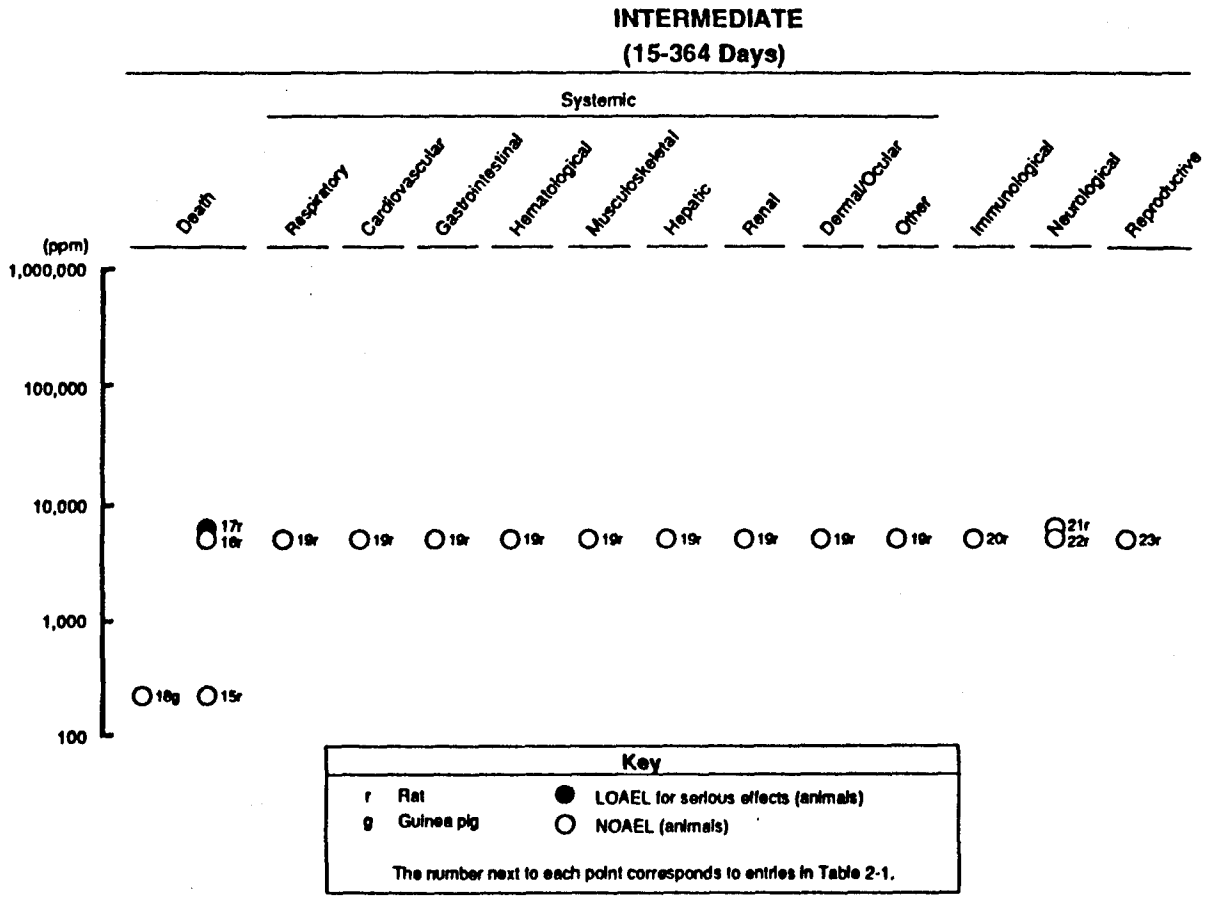


FIGURE 2-1 (Continued)



lungs were emphysematous. Rats seem to tolerate concentrations that are still high, but substantially lower than the acute exposures when exposed intermittently in intermediate duration studies. In a 90-day inhalation study, exposure of rats to 2-butanone concentrations of 5,000 ppm or less caused no signs of upper respiratory tract irritation or other respiratory effects (Cavender et al. 1983). Due to the irritation observed at 10,000 ppm in the study by Altenkirch et al. (1978a), the exposure concentration was reduced to 6,000 ppm and the study continued. All the rats died suddenly at 7 weeks with pathologically confirmed bronchopneumonia. This experiment was repeated and had the same results (Altenkirch et al. 1978b). Furthermore, rats exposed to n-hexane or a combination of n-hexane and 2-butanone did not develop bronchopneumonia, suggesting that a factor other than poor animal maintenance precipitated the bronchopneumonia. The Wistar rats used in this study may possibly have been derived from a stock that was particularly susceptible to infection. The initial exposure to a high concentration of 2-butanone may have weakened their immune system allowing infection to develop. No other studies were located that reported a link between 2-butanone exposure and bronchopneumonia in humans or animals.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after inhalation exposure to 2-butanone.

Histological examination of the hearts and aortae of rats exposed to 5,000 ppm or less of 2-butanone for 90 days revealed no exposure-related lesions (Cavender and Casey 1981; Cavender et al. 1983).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to 2-butanone.

No histopathological lesions were found in the esophagus, salivary glands, ileum, duodenum, jejunum, cecum, large or small intestines, or pancreas of rats exposed to 5,000 ppm or less of 2-butanone for 90 days(Cavender and Casey 1981; Cavender et al.1983).

Hematological Effects. Information regarding hematological effects of 2-butanone exposure in humans is limited to a case report in which a normal hematological profile and blood chemistry were found in an 18-year-old seaman exposed to 2-butanone while removing paint from an airplane hangar (Berg 1971). 2-Butanone exposure in this case was linked to retrobulbar neuritis and severely impaired vision. However, because methanol was found in the blood of the patient, consumption or exposure to methanol cannot be ruled out.

Studies in animals also indicate that 2-butanone does not produce hematological effects. No effect on hemoglobin concentration, or on red blood cell, white blood cell, neutrophil, lymphocyte, or monocyte populations were observed in rats exposed intermittently to 235 ppm 2-butanone for 12 weeks(LaBelle and Brieger 1955). Similarly, the hematological profile and serum

chemistry of rats exposed to 5,000 ppm or less of 2-butanone for 90 days were normal (Cavender et al. 1983).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to 2-butanone.

Histological examination of skeletal muscle and bone of rats exposed to 5,000 ppm or less of 2-butanone for 90 days revealed no exposure-related lesions (Cavender and Casey 1981; Cavender et al. 1983).

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to 2-butanone.

Most of the hepatic effects of inhalation exposure to 2-butanone observed in animals are minimal and probably not adverse, although acute exposure of guinea pigs to a high concentration (10,000 ppm) caused liver congestion (Patty et al. 1935). Exposure to 3,300 ppm had no effects. Serum alkaline phosphatase activity was not different in rats exposed intermittently to 300 ppm 2-butanone for 7 days compared to nonexposed control rats (Li et al. 1986). There was no change in the isozymes of cytochrome P-450 or in the total concentration of cytochrome P-450 in rats exposed to 800 ppm for 4 weeks(Toftgard et al. 1981). 2-Butanone, however, altered the metabolism of androstenedione by increasing the formation of two metabolites and decreasing the formation of two other metabolites. Furthermore, liver weight was increased in the 2-butanone-exposed rats (Toftgard et al. 1981). A small but statistically significant increase in absolute and relative liver weights of male and female rats, but no change in serum levels of hepatic enzymes (serum glutamic-oxaloacetic transaminase [SGOT], serum glutamic-pyruvic transaminase[SGPT], serum gamma-glutamyl transpeptidase [SGGT], and alkaline phosphatase)in male rats, was observed at an exposure level of 5,000 ppm for 90 days (Cavender et al. 1983). A significant increase only in alkaline phosphatase was noted in the female rats. Histopathological examination did not reveal any hepatic lesion aside from those expected in Fischer rats of this age. Exposure to 2,500 ppm 2-butanone had no effect on any hepatic parameter (Cavender et al. 1983). In the absence of histopathological liver lesions, the mild liver effects observed at 5,000 ppm were probably not adverse.

Renal Effects. No studies were located regarding renal effects in humans following inhalation exposure to 2-butanone.

Acute inhalation exposure of guinea pigs to 10,000 ppm 2-butanone resulted in congestion of the kidney (Patty et al. 1935). No effects were observed at 3,300 ppm. In an intermediate duration study, only minimal kidney effects were observed in rats exposed to 5,000 ppm or less (Cavender et al. 1983). Blood urea nitrogen determinations and urinalysis including urine volume, specific gravity, and pH showed that all values were within normal limits for male and female rats; the exception was that urine volume in the females was slightly but significantly increased. The kidney/body weight

ratio in male rats and the kidney/brain weight ratio in female rats were slightly but significantly elevated. Histopathological examination did not reveal any treatment-related renal lesion. In the absence of histopathological lesions or decrements in kidney function, these mild kidney effects do not appear to be adverse. No other studies were located regarding the renal effects of inhalation exposure to 2-butanone.

Dermal/Ocular Effects. Two men exposed to 2-butanone while removing paint from an airplane hangar had conjunctival irritation (Berg 1971). A third man had severe loss of vision. Within 36 hours, the man's vision was completely restored. However, because methanol was found in the blood of the man with vision loss, exposure to methanol cannot be ruled out. No other studies were located regarding dermal/ocular effects in humans following inhalation exposure to 2-butanone.

Guinea pigs exposed to 2-butanone. concentrations of 10,000 ppm or greater had eye irritation and lacrimation (Patty et al. 1935). Exposure to 100,000 ppm for 30 minutes or more caused cornea1 opacity. This condition gradually improved in guinea pigs that lived to 8 days after exposure. No effects occurred when guinea pigs were exposed to 3,300 ppm. Ophthalmological examination of the eyes and histological examination of the skin revealed no effects in rats exposed to 5,000 ppm or less of 2-butanone for 90 days (Cavender and Casey 1981; Cavender et al. 1983). No other studieswere located regarding dermal/ocular effects in animals following inhalation exposure to 2-butanone.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation exposure to 2 butanone.

In rats, no histopathological lesions were found in the thyroid, parathyroid, pituitary gland, adrenal glands, ears, or Zymbal glands of rats exposed to 5,000 ppm or less of 2-butanone for 90 days (Cavender and Casey 1981; Cavender et al. 1983). Furthermore, no specific effects on body weight were found.

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans following inhalation exposure to 2-butanone.

Although no specific tests for immunological effects were performed, histological examination of lymph nodes, thymus, spleen, and bone marrow of rats exposed to 5,000 ppm or less of 2-butanone for 90 days revealed no exposure-related lesions (Cavender and Casey 1981; Cavender et al. 1983). This NOAEL value is recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.4 Neurological Effects

In three separate studies, volunteers underwent a single 4-hour exposure to 200 ppm 2-butanone (Dick et al. 1984, 1988, 1989). No differences were observed between exposed and control groups on neurobehavioral tests including psychomotor tests (choice reaction time, visual vigilance, dual task, and memory scanning), postural sway, and a profile of mood states. No other studies were located regarding neurological effects after inhalation exposure to 2-butanone.

Neurological effects have been observed in animals exposed by inhalation to 2-butanone. Exposure of mice to 2-butanone at concentrations greater than or equal to 1,602 ppm for 4 hours caused a dose-related reduction in the duration of immobility in a "behavioral despair" swimming test (De Ceaurriz et al. 1983). The authors noted that the effect of 2-butanone was similar to that of antidepressants. In guinea pigs exposed acutely to 10,000 ppm 2-butanone, incoordination occurred within 90 minutes and unconsciousness occurred within 240-280 minutes (Patty et al. 1935). These signs occurred earlier at higher concentrations, but no neurological signs were observed at 3,300 ppm. Juvenile baboons exposed continuously to 100 ppm for 7 days showed early signs of narcosis, incoordination, and a loss of time perception in neurobehavioral tests (Geller et al. 1979). The neurological effects observed in this study could have resulted from narcosis. It is also possible that the baboons were distracted during the testing due to the irritating effects of 2-butanone on the respiratory system. Furthermore, the effects of 2-butanone observed at 100 ppm in the baboons do not imply that baboons are more sensitive to 2-butanone than other species tested. Since the baboons were evaluated with a complex discriminant behavioral task, it is possible that subtle neurobehavioral effects could be observed. However, it should be noted that only one exposure level was tested, only one baboon of four tested showed consistently different results from the controls throughout the study, and no statistical tests were performed. These limitations preclude definitive conclusions.

Intermediate duration exposures to 2-butanone were not neurotoxic in rats. Male Sprague-Dawley rats exposed continuously to 1,125 ppm 2-butanone for periods of 5 months or less showed no signs of peripheral neuropathy following histological examination (Saida et al. 1976). The neurotoxicity of n-butyl ketone, however, was markedly potentiated by 2-butanone. No differences were observed in nerve fiber preparations from male and female Fischer 344 rats exposed to 5,000 ppm or less 2-butanone for 90 days (Cavender and Casey 1981; Cavender et al. 1983). Furthermore, no histopathological lesions were found in the brain, sciatic nerve, tibia1 nerve, spinal cord, or optic nerves. No effects were observed in posture, gait, tone, and symmetry of the facial muscles, or in the pupillary, palpebral, extensor thrust, and cross-extensor thrust reflexes. The only effect recorded was a slight but statistically significant increase in brain weight in female rats exposed to 5,000 ppm. No clinical signs and no histological evidence of neuropathy in

peripheral nerves from the brachial plexus, sciatic nerve, spinal cord, and medulla were observed in rats exposed to 6,000 ppm for 7 weeks compared with rats exposed to n-hexane or a combination of n-hexane and 2-butanone(Altenkirch et al. 1978a). In contrast, 2-butanone potentiated the neurotoxicity of n-hexane. No neuropathological changes were found on light microscope and electron microscope examination of teased tail nerves after exposure of a rat to 200 ppm 2-butanone for 24 weeks (Takeuchi et al. 1983). At 4 weeks, significant increases in motor nerve conduction velocity and mixed nerve conduction velocity were found, while distal motor latency was decreased. These changes in nerve conduction velocity were not seen beyond 4 weeks. The transient increase in nerve conduction velocity may have been due to an effect of 2-butanone on the axonal membrane (Takeuchi et al. 1983). The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to 2-butanone.

Several studies in rats and mice were located regarding developmental effects after inhalation exposure. Exposure of pregnant rats to 1,000 or 3,000 ppm 2-butanone during gestation resulted in a slight increase in the incidence of malformations at 3,000 ppm; acaudia and imperforate anus were found in 2 fetuses out of 21 litters, and brachygnathia was noted in 2 other fetuses (Schwetz et al. 1974). A low incidence of sternebral anomalies was also noted in the 3,000 ppm group. Although the incidence of malformations was not high enough to support a positive correlation, it may have indicated a slight teratogenic effect in rats. A second study by the same group supported the previous findings of skeletal anomalies (Deacon et al. 1981). No statistically significant differences in external or soft tissue abnormalities were found in the offspring of dams exposed to 3,000 ppm or less during gestation, No effect was observed on the number of live fetuses/litter or on fetal crown-rump length. Skeletal abnormalities, including delayed ossification of the cervical centra, sternebral malformations, and asymmetric pelvis were observed at 3,000 ppm. Decreased body weight gain and increased water consumption in the pregnant rats at 3,000 ppm 2-butanone indicated that some maternal toxicity may have occurred at this exposure level. Deacon et al. (1981) concluded 2-butanone was slightly fetotoxic, but not embryotoxic or teratogenic at 3,000 ppm. Mean fetal body weight was reduced in the male and female offspring of mouse dams exposed to 3,000 ppm butanone, but was significantly reduced only in the males(Mast et al. 1989). A statistically significant increase in the incidence of misaligned sternebrae was observed in the 3,000 ppm group. No effects were observed at 1,000 ppm. Thus, 2-butanone was fetotoxic in both rats and mice. In pregnant rats, continuous exposure to 800 ppm 2-butanone throughout gestation resulted in the failure of three of eight of the rats to deliver

litters. While all 8 of the control dams in the experiment for 2-butanone delivered litters, 6 of 16 control dams in an experiment with n-hexane in the same study also failed to produce litters. Therefore, the reliability of the results in the 2-butanone exposed group is questionable (Stoltenburg-Didinger et al. 1990). The reliable NOAEL and LOAEL values for developmental effects are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to 2-butanone.

Although no tests for reproductive function were performed, histological examination of the testes, epididymides, seminal vesicles, vaginas, cervices, uteri, oviducts, ovaries, or mammary glands of rats exposed to 5,000 ppm or less of 2-butanone for 90 days revealed no exposure-related lesions (Cavender and Casey 1981; Cavender et al. 1983).

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to 2-butanone.

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

Two retrospective studies of industrial workers chronically exposed to 2-butanone in dewaxing plants reported that deaths due to cancer were less than expected. In a cohort of 446 males employed by Shell Chemical Company, 13 deaths were due to cancer, whereas 14.26 were expected; the standard mortality ratio (SMR) was 0.91 (Alderson and Rattan 1980). In the same cohort, 2 cases of buccal or pharyngeal neoplasms were found; 0.13 were expected to exist, and the' SMR was 15.38. There were 4 cases of stomach, colon, or rectal cancer; 3.18 were expected, and the SMR was 1.28. The incidence of buccal or pharyngeal neoplasms was statistically significant but was regarded by the authors as due to chance because of the small number of individuals affected and the number of separate comparisons made between observed and expected rates. Furthermore, the use of tobacco was not discussed in this study. The incidence of stomach, colon, or rectal cancer was not statistically significant. The authors concluded that there was no clear evidence of a cancer hazard at this dewaxing plant. A retrospective cohort study of 1,008 male oil refinery workers occupationally exposed to an estimated 1-4 ppm of 2-butanone in a dewaxing-lubricating oil plant was also conducted (Wen et al. 1985). The overall cancer-related mortality was less than expected. The increased incidence of buccal and pharyngeal neoplasms reported by Alderson and Rattan (1980) was not confirmed in this study.

No studies were located regarding cancer in animals following inhalation exposure to 2-butanone.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death of humans following oral exposure to 2-butanone.

Oral LD_{50} values for 2-butanone were similar (approximately 2,737 mg/kg) in three groups of Sprague-Dawley rats: immature (14 days old), young adult(80-160 g), and older adult (300-470 g) (Kimura et al. 1971). The oral LD_{50} could not be determined in newborn rats because of volume limitations; it was estimated to be less than 805 mg/kg, Most of the Sprague-Dawley rats receiving 3,670, 7,340, or 14,680 mg/kg by gavage died within 1 hour at each dose, except 1 male and 1 female at the lowest dose; these rats survived until sacrifice at 14 days (Stillmeadow Inc. 1978). The data were insufficient for determination of an LD_{50}, but the authors estimated the acute oral LD_{50} to be less than 3,670 mg/kg, which is in agreement with the data reported in Kimura et al. (1971). The LD_{50} in Carworth-Wistar rats was 5,522 mg/kg (Smyth et al. 1962), which may represent a strain difference. In two separate experiments, 1,080 mg 2-butanone/kg administered by gavage in corn oil produced no deaths in male Fischer rats (Brown and Hewitt 1984) or in male Sprague-Dawley rats(Hewitt et al. 1983). Tanii et al. (1986) determined the oral LD_{50} for 2-butanone in mice as 4,044 mg/kg (95% confidence limits - 3,200-5,111 mg/kg). The acute duration LD_{50} values and the LOAEL value for death in rats are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

The systemic effects of 2-butanone after oral exposure are discussed below. No studies were located regarding gastrointestinal, hematological, musculoskeletal, or dermal/ocular effects in humans or animals after oral exposure to 2-butanone. The highest NOAEL values and all reliable LOAEL values for each systemic effect after oral exposure in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. One clinical report of oral exposure to 2-butanone in humans was located. A 47-year-old woman accidentally ingested an unknown volume of 2-butanone that had been stored in a rum bottle (Kopelman and Kalfayan 1983). She was admitted to an emergency ward unconscious and hyperventilating. Blood gases were 85 mmHg oxygen and 24 mmHg carbon dioxide. Analysis of her blood showed a 2-butanone plasma concentration of 95 mg/lOO mL. Slow infusion of sodium bicarbonate reduced the hyperventilation, and blood gases improved to 78 mmHg oxygen and 25 mmHg carbon dioxide. Within 12 hours, she had regained consciousness, made an

TABLE 2-2. Levels of Significant Exposure to 2-Butanone - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(G)	1 d				5,522 (LD_{50})	Smyth et al. 1962
2	Rat	(G)	1 d				3,670 (8/10 died)	Stillmeadow Inc. 1978
3	Rat	(G)	1 d				2,737 (LD_{50})	Kimura et al. 1971
4	Mouse	(G)	1 d				4,044 (LD_{50})	Tanii et al. 1986
Systemic								
5	Rat	(G)	1 d	Hepatic Renal	1,080	1,080 (tubular necrosis)		Brown and Hewitt 1984
6	Rat	(GO)	1 d 1x/d	Hepatic	1,080			Hewitt et al. 1990
7	Rat	(GW)	3 d 1x/d	Hepatic	1,130			Raunio et al. 1990
8	Rat	(GW)	1-7 d 1x/d	Hepatic	1,500			Robertson et al. 1989
9	Rat	(G)	1 d 1x/d	Hepatic	1,500			Traiger et al. 1989
10	Rat	(GO)	1 d 1x/d	Hepatic	1,080			Brady et al. 1989
Neurological								
11	Rat	(G)	1 d				3,670 (CNS depression)	Stillmeadow Inc. 1978

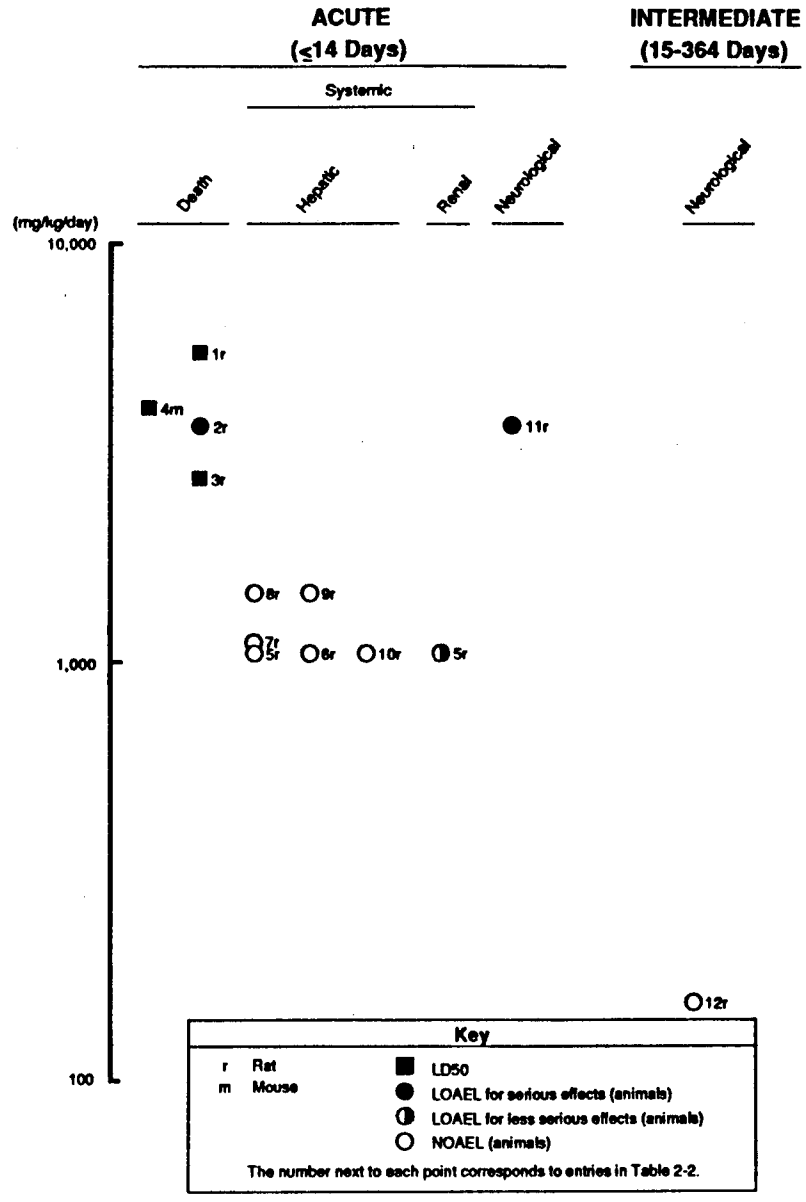
TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
INTERMEDIATE EXPOSURE								
Neurological								
12	Rat	(G)	13 wk 5 d/wk		173			Ralston et al. 1985

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

CNS = central nervous system; d = day; (G) = gavage (undiluted); LD_{50} = lethal dose 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; wk = week(s)

FIGURE 2-2. Levels of Significant Exposure to 2-Butanone - Oral



uneventful recovery over the next few days, and was discharged after 1 week(Kopelman and Kalfayan 1983).

All albino rats receiving 3,670 mg/kg or more had labored breathing, and most of them died within 1 hour (Stillmeadow Inc. 1978). It is'not clear whether the labored breathing represented a respiratory or a neurological response to a high dose. No other studies were located regarding respiratory effects after oral exposure to 2-butanone.

Cardiovascular effects. Cardiovascular effects observed in a 47-year-old woman after accidental ingestion of 2-butanone were decreased blood pressure and increased pulse rate (Kopelman and Kalfayan 1983). No other reports were located regarding cardiovascular effects in humans following oral exposure to 2-butanone.

No studies were located regarding cardiovascular effects in animals following oral exposure to 2-butanone.

Hepatic Effects. No studies were located regarding hepatic effects in humans following oral exposure to 2-butanone.

2-Butanone had no effect on liver weight, SGPT, or serum ornithine carbamyl transferase activities measured 42 hours after oral exposure of rats to 1,080 mg/kg (Hewitt et al. 1983). Similarly, Brown and Hewitt (1984)observed normal SGPT activity in rats exposed orally to 1,080 mg 2-butanone/kg. Although histological examination was not performed, 2-butanone appears to have a low order of hepatic toxicity in inhalation studies. Several studies have shown that 2-butanone has the ability to induce microsomal liver enzymes. Acute oral treatment of rats with 2-butanone at doses of 1,080 to 1,500 mg/kg/day for l-7 days resulted in increased levels of cytochrome P-450, increased activities of cytochrome P-450-dependent monooxygenases (Brady et al. 1989; Raunio et al. 1990; Robertson et al. 1989; Traiger et al. 1989) and proliferation of the smooth endoplasmic reticulum(Traiger et al. 1989). In the absence of clinical or histological evidence of liver damage, induction of microsomal enzymes probably represents a normal physiological response to xenobiotics rather than an adverse effect. Furthermore, oral treatment of rats with 1,080 mg/kg 2-butanone had no effect on the fragility of hepatic lysosomes or on the calcium uptake by mitochondria or microsomes (Hewitt et al. 1990). Therefore, the doses of 1,080-1,500 mg/kg can be considered acute oral NOAEL values for hepatic effects.

Renal Effects. No studies were located regarding renal effects in humans following oral exposure to 2-butanone.

Oral exposure of rats to 1,080 mg 2-butanone/kg caused mild renal tubular necrosis but had no effect on renal organic ion transport(PAH, TEA) or plasmacreatinine (Brown and Hewitt 1984). No other studies were located regardingrenal effects in animals after oral exposure to 2-butanone.

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to 2-butanone.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to 2-butanone.

In animals, clinical signs of central nervous system toxicity including lethargy, labored breathing, ptosis, lacrimation, exophthalmos, ataxia, salivation, and piloerection were observed in rats treated by gavage with 2-butanone at doses greater than or equal to 3,670 mg/kg (Stillmeadow Inc.1978). Most of these rats died. No effect was observed on neurobehavioral tests including hindlimb grasp, hindlimb place, balance beam, and roto-rod in rats treated by gavage with 2-butanone at a time-weighted average dose of 173 mg/kg/day for 90 days (Ralston et al. 1985). No other studies were located regarding neurological effects in animals after oral exposure to 2-butanone. The NOAEL value and LOAEL value for neurological effects are recorded in Table 2-2 and plotted in Figure 2-2.

No studies were located regarding the following health effects in humans or animals after oral exposure to 2-butanone:

2.2.2.5 Developmental Effects
2.2.2.6 Reproductive Effects
2.2.2.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals after oral exposure to 2-butanone.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to 2-butanone. One study reported the dermal LD_{50} for 2-butanone in rabbits to be greater than 10 mL/kg (Smyth et al. 1962). No other studies were located regarding death in animals after dermal exposure to 2-butanone.

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-butanone.

The only systemic effects of dermal exposure studied were dermal and ocular. The highest NOAEL value and all reliable LOAEL values for dermal and ocular effects in each species and duration category are recorded in Table 2-3.

Dermal/Ocular Effects. Application of 0.1 mL undiluted 2-butanone once daily for 18 days to the volar forearm of volunteers did not result in erythema, increase in skin-fold thickness, or edema over the 18-day exposure period Wahlberg (1984). Further details regarding the number of volunteers were not reported.

In rabbits and guinea pigs, application of undiluted 2-butanone caused minimal skin irritation, erythema, and/or increase in skin-fold thickness (Anderson et al. 1986; Hazleton Laboratories 1963a; Wahlberg 1984). Slight desquamation occurred in guinea pigs after 31 weeks of dermal exposure to increasing amounts of 2-butanone (Eastman Kodak 1978). Abraded skin areas were slightly more sensitive to the application of 2-butanone (Hazleton Laboratories 1963a).

2-Butanone instilled into the conjunctival sac of rabbits caused irritation, cornea1 opacity, and conjunctivitis (Davis and Baker 1975; Haskell Laboratories 1971; Hazleton Laboratories 1963b; Kennah et al. 1989). These effects were generally reversible in 7-14 days. Hazleton Laboratories (1963b) reported that one of six rabbits had persistent cornea1 damage after 7 and 14 days. On the basis of Draize scores in these studies, 2-butanone was classified as moderately irritating.

2.2.3.3 Immunological Effects

One clinical report of 2-butanone-evoked contact urticaria was located. A 48-year-old man employed as a painter complained of severe irritation when he handled 2-butanone (Varigos and Nurse 1986). A small amount of 2-butanone applied to his forearm produced a bright red area at the site of application. The area became itchy, but no induration or edema was noted. After 15 minutes, the reaction subsided. Two days later, the test was repeated with the same result. Five volunteers were later tested for sensitivity to 2-butanone by the same method, but no response was observed.

No studies were located regarding immunological effects in animals after dermal exposure to 2-butanone.

TABLE 2-3. Levels of Significant Exposure to 2-Butanone - Dermal

Species	Exposure frequency/ duration	System	NOAEL	LOAEL (effect)		Reference
				Less serious	Serious	
ACUTE EXPOSURE						
Systemic						
Rabbit	24 hr	Derm/oc		0.5 mL (erythema)		Hazleton Laboratories 1963a
Rabbit	1 d	Derm/oc			0.1 mL (corneal damage)	Hazleton Laboratories 1963b
Rabbit	1 d	Derm/oc	0.03 mL	0.1 mL (irritation, corneal thickening)		Kennah et al. 1989
Gn pig	3 d 3/d	Derm/oc		10 $\mu L/cm^2$ (erythema)		Anderson et al. 1986
Gn pig	10 d 1/d	Derm/oc		0.1 mL (skin-fold thickening)		Wahlberg 1984
INTERMEDIATE EXPOSURE						
Systemic						
Human	18 d 1/d	Derm/oc	0.1 mL			Wahlberg 1984

d = day; Derm/oc = dermal/ocular; Gn pig = guinea pig; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after dermal exposure to 2-butanone.

In an intermediate study of dermal exposure, 1-2 mL of undiluted 2-butanone was applied in increasing amounts to shaved areas on the backs of guinea pigs 5 days/week for 31 weeks or less (Eastman Kodak 1978). No clinical signs of neurotoxicity were observed. No evidence of neurotoxicity was noted on examination of Epon sections of the medulla oblongata and tibia1 nerve by light microscopy (Eastman Kodak 1978). The details of 2-butanone application, however, were not clear in this report.

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

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2-4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to 2-butanone.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

2-Butanone is well absorbed during inhalation exposure. Pulmonary uptake in humans ranged from 41% to 56% of the inspired quantity (Liira et al. 1988a, 1988b, 1990). Exercise increased the pulmonary uptake due to the greater ventilatory rate (Liira et al. 1988b). The high blood/air solubility ratio of 2-butanone also favors absorption (Saida et al. 1976; Perbellini et al. 1984). Several investigators have reported that exposure concentrations of Z-butanoneare significantly correlated with blood concentrations in humans (Brown et al. 1986; Brugnone et al. 1983; Ghittori et al. 1987; Liira et al. 1988a, 1988b;Lowry 1987; Miyasaka et al. 1982; Perbellini et al. 1984; Tolos et al. 1987). Exposure of humans to 200 ppm 2-butanone for 4 hours resulted in blood concentrations of 3.5-7.2 μg/mL (Liira et al. 1988a, 1988b; Lowry 1987). Occupational concentrations are significantly correlated with blood and urine concentrations of unmetabolized 2-butanone (Brugnone et al. 1983; Ghittori et al. 1987; Miyasaka et al. 1982). Blood levels of 2-butanone are also

significantly correlated with breath levels (Brown et al. 1986). These data indicate that 2-butanone is absorbed upon inhalation.

Information on the absorption of 2-butanone by animals after inhalation exposure is limited. Rats that were exposed to 600 ppm 2-butanone for 6 hours on 1 day or for 6-10 hours/day for 8 days had blood concentrations of 1,041 μmol/L after a single exposure and 1,138 μmol/L after repeated exposure(Liira et al. 1991). The similarity in blood concentrations after single and repeated intermittent exposure indicates that 2-butanone does not accumulate.

2.3.1.2 Oral Exposure

A woman who had metabolic acidosis after having accidentally ingested 2-butanone stored in a rum bottle had a blood concentration of 95 mg/lOO mL(13.2 mM) (Kopelman and Kalfayan 1983). A man who intentionally ingested 100 mL of liquid cement containing a mixture of acetone (18%), 2 butanone (28% or about 37 mg/kg), and cyclohexanone (39%) had a plasma level of 2-butanone of about 110 μg/mL at 5 hours after ingestion (Sakata et al. 1989). These reports provide qualitative evidence that 2-butanone is absorbed following oral exposure in humans, but do *not* provide information regarding the extent of absorption. In the first case, the quantity ingested was unknown, while in the second case, the man was treated by gastric lavage at 2 hours after ingestion.

Oral administration (gavage) of 1,690 mg 2-butanone/kg in rats resulted in a plasma concentration of 94 mg/lOO mL at 4 hours (Dietz and Traiger 1979). Within 18 hours, the plasma concentration decreased to 6.2 mg/lOO mL (Dietzand Traiger 1979). A second, similar experiment in rats showed that, after oral administration of 1,690 mg 2-butanone/kg, the plasma concentration was 95 mg/lOO mL; the concentration decreased to 7 mg/lOO mL by 18 hours (Dietz et al. 1981). These data indicate that 2-butanone is rapidly absorbed and eliminated after oral administration.

2.3.1.3 Dermal Exposure

No studies were located regarding the rate or extent of absorption of 2-butanone in humans or animals following dermal exposure.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding the distribution of 2-butanone following inhalation exposure in humans.

In vitro determinations of the 2-butanone tissue/air solubility ratio for human kidney, liver, muscle, lung; heart, fat, and brain show that the solubility is similar in all tissues, and that the ratio is nearly equal to

200 (Perbellini et al. 1984). Blood/tissue solubility ratios are all near unity; therefore, 2-butanone is not expected to concentrate in any one tissue(Perbellini et al. 1984).

Information regarding distribution of 2-butanone in animals after inhalation exposure is limited. Rats that were exposed to 600 ppm 2-butanone for 6 hours on 1 day or for 6-10 hours/day for 8 days had blood concentrations of 1,041 μmol/L after a single exposure and 1,138 μmol/L after repeated exposure (Liira et al. 1991). The concentration of 2-butanone in perirenal fat was 0.71 μmol/g after a single exposure and 0.70 μmol/g after repeated exposure. The similarity in blood and perirenal concentrations after single and repeated intermittent exposure indicates that 2-butanone does not accumulate.

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of 2-butanone following oral exposure in humans or animals.

2.3.2.3 Dermal Exposure

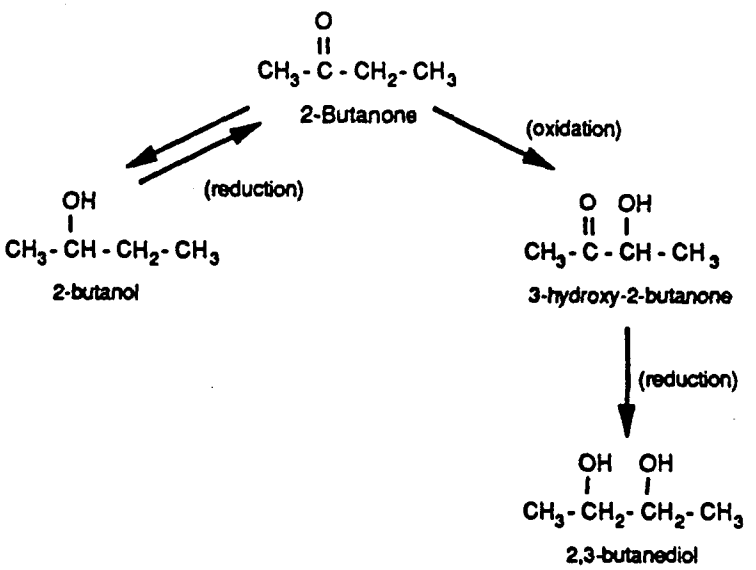
No studies were located regarding the distribution of 2-butanone following dermal exposure in humans or animals.

2.3.3 Metabolism

Few studies exist regarding the metabolism of 2-butanone in humans. Two metabolites of 2-butanone have been identified in human urine after inhalation exposure. They are 3-hydroxy-2-butanone (Brugnone **et** al. 1983; Perbellini et al. 1984) and 2,3-butanediol (Liira et al. 1988a, 1988b, 1990). The urinary concentrations of these metabolites, however, represent only about 0.1%-2% of the absorbed 2-butanone. P-Butanol was found in the blood of male volunteers exposed to 200 ppm 2-butanone for 4 hours (Liira et al. 1990). In addition to 3-hydroxy-2-butanone and 2,3-butanediol, a third metabolite, 2-butanol, has been found in the blood in guinea pigs (DiVincenzo et al. 1976)and rats (Dietz et al. 1981). About 30% of the 2-butanone administered orally in rats was converted to 2,3-butanediol; 4% was converted to 2-butanol, and 4% was converted to 3-hydroxy-2-butanone (Dietz et al. 1981).

In guinea pigs, 2-butanone was metabolized by both oxidative and reductive pathways (Figure 2-3). Oxidation produces 3-hydroxy-2-butanone, which is then reduced to 2,3-butanediol (DiVincenzo et al. 1976). Reduction of 2-butanone produces 2-butanol. The metabolites of 2-butanone in guinea pigs were excreted in the urine as 0-glucuronides or O-sulfates.

FIGURE 2-3. Proposed Metabolic Pathways for 2-Butanone*



*Adapted from DiVincenzo et al. 1976

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Urinary excretion of unchanged 2-butanone and its metabolites, 3-hydroxy-2-butanone and 2,3-butanediol, accounts for only 5% or less of the 2-butanone absorbed by inhalation in humans (Liira et al. 1988a, 1990;Perbellini et al. 1984). Unchanged 2-butanone is excreted primarily through the lungs; the quantity eliminated by this route is an estimated 20X-40% (Browning 1965; Riihimaki 1986); however, only about 3% of absorbed 2-butanone was excreted unchanged in the expired air of humans exposed to 200 ppm for 4 hours (Liira et al. 1988a, 1990). 2-Butanone is rapidly cleared from the blood with a reported plasma half-life in humans of 49-96 minutes (Brown et al. 1986; Liira et al. 1988a; Lowry 1987) and an apparent clearance rate of 0.60 L/minute (Liira et al. 1990). Therefore, 2-butanone would not be expected to accumulate with chronic exposure (Lowry 1987).

No studies were located regarding excretion of 2-butanone in animals after inhalation exposure.

2.3.4.2 Oral Exposure

Information regarding the excretion of 2-butanone after oral exposure in humans is limited. A man who intentionally ingested 100 mL of liquid cement containing a mixture of acetone (18X), 2-butanone (28% or about 37 mg/kg), and cyclohexanone (39%) had a plasma level of 2-butanone of about 110 μg/mL at 5 hours after exposure (Sakata et al. 1989). The plasma level declined to about 95 μg/mL at 12 hours and to <20 μg/mL at 18 hours, where it remained until about 25 hours and slowly declined to <5 μg/mL at 48 hours. Urine levels of 2-butanone decreased gradually from 123 μg/mL at 5 hours to 61 μg/mL at 19 hours. Disappearance from the urine then became more rapid with about 10 μg/mL excreted at 48 hours. While this study provided information on the elimination of 2-butanone from plasma and urine of a human orally exposed, coexposure to the other components of the cement could have influenced the elimination.

No studies were located regarding the rate or extent of excretion of 2-butanone in animals following oral exposure.

2.3.4.3 Dermal Exposure

No studies were located regarding the rate or extent of excretion of 2-butanone in humans or animals following dermal exposure.

2.4 RELEVANCE TO PUBLIC HEALTH

The only known effects of 2-butanone in humans are related to its irritating properties on the respiratory and dermal/ocular systems. Effects

observed in animals include death, irritation of respiratory tissue, eyes, and skin, liver congestion, kidney congestion, cornea1 opacity, narcosis and incoordination, and fetotoxicity.

No acute-, intermediate-, or chronic-duration inhalation MRLs were derived for 2-butanone. In the case of acute-duration inhalation exposure, target organs have not been sufficiently identified. Intermediate-duration inhalation studies likewise failed to identify target organs, and nose and throat irritation occurred in humans exposed for 5 minutes to exposure levels that were much lower than NOAEL values in animals in intermediate-duration studies. No studies were located regarding toxic effects in humans or animals after chronic inhalation exposure, precluding the derivation of a chronic inhalation MRL. No acute, intermediate-, or chronic-duration oral KRLs were derived for 2-butanone. In the case of acute-duration oral exposure, target organs have not been sufficiently identified. The paucity of information on toxic effects after intermediate- and chronic-duration oral exposure likewise precludes the derivation of MRLs for these durations. Acute-duration, intermediate-duration, and chronic-duration dermal MRLs were not derived for 2-butanone due to the lack of appropriate methodology for the development of dermal MRLs.

Death. No studies were located regarding death of humans after inhalation, oral, or dermal exposure to 2-butanone. Death of rats and mice occurred within a few hours during acute inhalation exposure to very high concentrations (greater than or equal to 90,000 ppm) (Klimisch 1988; LaBelle and Brieger 1955). The inhalation 4-hour LC_{50} in rats was 11,700 ppm (LaBelle and Brieger 1955). In the intermediate-duration studies, no rats died after exposure to 5,000 ppm or less for 6 hours/day, 5 days/week for 90 days(Cavender et al. 1983), but all rats exposed to 6,000 ppm, 8 hours/day, 7 days/week died from bronchopneumonia (Altenkirch et al. 1978a, 1978b). The bronchopneumonia may have been caused by the 2-butanone exposure because the results were reproducible and did not occur in rats exposed to n-hexane or the combination of 2-butanone and n-hexane (Altenkirch et al. 1978a, 1978b). The concentration of 2-butanone that would cause death in humans after inhalation is not known. It does not seem likely that humans would be exposed to the high concentrations that are fatal to animals except in an occupational accident. 2-Butanone has a half-life in air of only 14 hours; therefore, in the vicinity of toxic waste sites, ambient concentrations would be expected to be low.

Information regarding death from oral and dermal exposure is limited to LD_{50} determinations. Oral LD_{50} values have been reported to be approximately 2,740 mg/kg *in* immature, young adult, and older Sprague-Dawley rats (Kimura et al. 1971), 5,542 mg/kg in Wistar rats (Smyth et al. 1962), and 4,044 mg/kg in mice (Tanii et al. 1986). The dermal LD_{50} in rabbits is greater than 10 mL/kg (Smyth et al. 1962). Oral exposure of humans to 2-butanone might occur through drinking water if this chemical seeped from a waste site, for example, into the groundwater. 2-Butanone is highiy water soluble and is

expected to have a high soil mobility. Exposure through drinking water is,therefore, possible, but fatal concentrations are unlikely Dermalexposure of humans is unlikely to result in death.

Systemic Effects. There are few known systemic effects of 2-butanone exposure in humans. Three men exposed to 2-butanone vapors while removing paint from an airplane hangar developed mild respiratory symptoms; however, the nature and extent of these symptoms were not described (Berg 1971). One of the men suffered a loss of vision secondary to retrobulbar neuritis, but this was reversed within 36 hours. Furthermore, exposure to methanol could not be ruled out. Nelson et al. (1943) reported that 100 ppm 2-butanone caused slight nose and throat irritation, and that some subjects complained of mild eye irritation at 200 ppm. Subjects could not tolerate 350 ppm 2-butanone. For this study, it was estimated that 200 ppm would be the maximum concentration of 2-butanone tolerable for an 8-hour exposure period. No adverse effects were reported in several studies exposing volunteers to 200 ppm 2-butanone for 4 hours (Dick et al. 1984, 1988, 1989; Liira et al. 1988a, 1988b). In contrast, sporting goods manufacturing plant workers exposed to 250 ppm or less complained of skin, eye, nose, and throat irritation, and central nervous system symptoms (headache, dizziness, fatigue)(Lee and Murphy 1982). One worker in this group complained of "acting differently," but the change in behavior was not described. These exposures were in enclosed areas with poor ventilation. Exposure at the sporting goods factory was not to 2-butanone exclusively; other solvent vapors were also present. Therefore, the central nervous system symptoms described may not have been due solely to 2-butanone.

Respiratory Effects. The respiratory effects observed in humans are discussed above. Upper respiratory tract irritation was reported in rats exposed for a few hours to 10,000 ppm 2-butanone (Altenkirch et al. 1978a). After the concentration was lowered to 6,000 ppm, all the rats died suddenly at 7 weeks. Bronchopneumonia was confirmed pathologically as the cause of death. In contrast, no respiratory tract irritation or infection was observed in rats,exposed to 5,000 ppm 2-butanone for 90 days (Cavender et al. 1983). Patty et al. (1935) reported that acute inhalation exposure of guinea pigs to 10,000 ppm or more of 2-butanone produced gasping respiration, emphysematous lungs, ocular irritation, and lacrimation. Exposure to 100,000 ppm for 30 minutes or more caused cornea1 opacity, a condition which gradually improved in guinea pigs that lived 8 days after exposure. Since 2-butanone exposure is not tolerable to humans at concentrations of 350 ppm (Nelson et al. 1943), it is highly unlikely that inhalation exposure could result in respiratory, dermal, or ocular effects more serious than minor irritation. Dermal exposure of humans, rabbits, and guinea pigs has produced irritation to the skin (Anderson et al. 1986; Hazleton Laboratories 1963a; Wahlberg 1984). Intraocular exposure of rabbits has resulted in cornea1 damage (Hazleton Laboratories 1963b; Kennah et al. 1989). Dermal and eye contact with liquid 2-butanone is possible in occupational settings and at hazardous waste sites.

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation, oral, or dermal exposure to 2-butanone. Animal data indicate that hepatic effects after high-level exposure to 2-butanone would be minimal in humans. Liver congestion was found in guinea pigs exposed acutely by inhalation to 10,000 ppm or more (Patty et al. 1935). Serum concentrations of hepatic enzymes were not changed in rats after 2-butanone exposures of 300-5,000 ppm for l-12 weeks (Cavender et al. 1983; Li et al. 1986; Schwetz et al. 1974). No lesions that could be linked to 2-butanone exposure were found following histological examination, although a slight increase in absolute and relative liver weight was noted (Cavender et al. 1983). After exposure of rats to 800 ppm 2-butanone for 5 weeks, no changes were observed in the content of hepatic cytochrome P-450 or in the cytochrome P-450 isozyme profile (Toftgard et al. 1981). 2-Butanone, however, altered the metabolism of androstenedione by increasing the formation of two metabolites and decreasing the formation of two other metabolites. Furthermore, liver weight was increased in the 2-butanone-exposed rats (Toftgard et al. 1981). While no induction of microsomal enzymes was found in rats exposed to 2-butanone by inhalation, several studies have shown that E-butanone has the ability to induce microsomal liver enzymes in rats after acute oral exposure (Brady et al. 1989; Raunio et al. 1990; Robertson et al. 1989; Traiger et al. 1989). These studies also suggested that 2-butanone potentiates the toxicity of other chemicals, such as, carbon tetrachloride, n-hexane, m-xylene, and chloroform, by increasing their metabolism to toxic metabolites. While enzyme induction by itself represents a normal physiological response to a xenobiotic rather than an adverse effect, the enzyme induction by 2-butanone can be viewed as an adverse effect if coexposure to other chemicals for which 2-butanone potentiates toxicity by this mechanism occurs. Therefore, humans working or living near hazardous waste sites where these chemicals are present along with 2-butanone may be at greater risk of adverse hepatic effects.

Renal Effects. Renal effects of 2-butanone exposure in humans would probably be minimal based on animal data. Kidney congestion was found in guinea pigs exposed acutely by inhalation to 10,000 ppm or more (Patty et al. 1935). Cavender et al. (1983) assessed kidney function with measurements of blood urea nitrogen, urine volume, urine specific gravity, and pH after a go-day exposure to 5,000 ppm 2-butanone. All values were within normal ranges, and no histopathological lesions attributable to 2-butanone exposure were found. Oral exposure of rats to 1,080 mg 2-butanone/kg caused mild renal tubule necrosis but had no effect on renal organic ion transport or plasma creatinine; therefore, in spite of mild necrosis, normal kidney functions were not impaired. Exposure of humans to 2-butanone at hazardous waste sites is, therefore, not likely to result in severe kidney effects.

Neurological Effects. The main neurological complaints of humans exposed occupationally to 2-butanone are headaches, dizziness, nausea, and fatigue (Lee and Frederick 1981; Lee and Parkinson 1982). However, these symptoms were not reported in several inhalation studies in which humans were exposed to 200 ppm of 2-butanone for 4 hours (Dick et al. 1984, 1988, 1989; Liira

et al. 1988a, 1988b). In the occupational exposures cited, 2-butanone was combined with several other solvents; therefore, a neurological effect exclusive to 2-butanone cannot be inferred. Dick et al. (1984, 1988, 1989) found that exposure to 2-butanone had no effect on any neurobehavioral measurement. Nevertheless, early signs of narcosis and incoordination based on a battery of neurobehavioral tests were described in juvenile baboons after continuous exposure to 100 ppm 2-butanone for 7 days (Geller et al. 1979). It is also possible that the baboons were distracted during testing by the irritant effects of 2-butanone on the respiratory tract and were not, as the investigators concluded, in a state of narcosis.

Narcosis and incoordination were also observed in guinea pigs exposed to 10,000 ppm or more 2-butanone in air for a few hours (Patty et al. 1935). 2-Butanone was not neurotoxic at lower concentrations in longer duration studies in animals. Rats continuously exposed to 1,125 ppm for 5 months showed no signs of peripheral neuropathy on histological examination (Saida et al. 1976). Altenkirch et al. (1978a) observed no clinical signs of neuropathy in rats exposed for 7 weeks to 6,000 ppm. No neurological effects were observed in rats exposed by inhalation to\ 5,000 ppm for 90.days (Cavender et al. 1983). Alterations in nerve conduction velocity were seen in rats exposed by inhalation for 4 weeks to 200 ppm 2-butanone (Takeuchi et al. 1983). The toxicological significance of this observation is questionable because normal nerve conduction velocities were observed at all time points beyond 4 weeks. No neurological effects were observed in rats after oral exposure to 1,725 mg/kg for 90 days (Ralston et al. 1985). Therefore, exposure of humans to 2-butanone alone in the workplace or at hazardous waste sites is not likely to result in serious neurological effects.

Although exposure to 2-butanone appears relatively innocuous, this ketone is very hazardous in combination with other solvents. 2-Butanone markedly potentiates the neurotoxicity of ethanol, n-hexane, methyl-n-butyl ketone, and ethyl-n-butyl ketone (Altenkirch et al. 1977; Cunningham et al. 1989; King et al. 1985; Ralston et al. 1985; Robertson et al. 1989; Vallat et al. 1981). Glue formulations containing both 2-butanone and n-hexane caused "glue sniffers' neuropathy" (Altenkirch et al. 1977; King et al. 1985; Vallat et al. 1981). This neuropathy is characterized by motor nerve dysfunction, paresis, paralysis, muscular atrophy, and neural tissue morphology changes including paranodal axon swelling, neurofilamentous hyperplasia, and demyelination (see Section 2.6). Therefore, humans working or living near hazardous waste sites where methyl-n-butyl ketone, ethyl-n-butyl ketone, or n-hexane is present or who frequently use alcohol may be at greater risk for neurological effects if 2-butanone is also present.

Developmental Effects. No studies were located regarding developmental effects in humans following inhalation, oral, or dermal exposure to 2-butanone. Inhalation exposure of rats and mice to 3,000 ppm during gestation resulted in fetotoxic effects, such as reduced fetal weight, skeletal variations, and delayed ossification (Deacon et al. 1981; Mast et al.

1989; Schwetz et al. 1974). It is not known whether exposure of humans to 2-butanone by any route would result in fetotoxic effects, but the presence of these effects in two animal species strongly suggests that such effects might occur in humans.

Reproductive Effects. No studies were located regarding reproductive effects in humans following inhalation, oral, or dermal exposure to 2-butanone. The only study regarding reproductive effects in animals was a go-day inhalation study in rats exposed to 5,000 ppm or less of 2-butanone (Cavender and Casey 1981; Cavender et al. 1983). Histological examination of male and female reproductive organs revealed no effects, but reproductive function was not tested.

Genotoxic Effects. *In vivo* and in vitro studies regarding the genotoxicity of 2-butanone are summarized in Table 2-4. No induction of micronuclei was found in the erythrocytes of mice (O'Donoghue et al. 1988) or hamsters (Basler 1986) after intraperitoneal injection with 2-butanone. &I vitro studies sponsored by the Chemical Manufacturers' Association showed that 2-butanone was not mutagenic in the Salmonella/mammalian-microsome preincubation mutagenicity assay (Ames test) or the L5178Y TK +/- mouse lymphoma mutagenesis assay with or without activation (O'Donoghue et al. 1988). 2-Butanone did not induce unscheduled DNA synthesis in rat primary hepatocytes, and it did not transform BALB/3T3 cells. 2-Butanone did not increase the reverse mutation frequency in Escherichia coli or Salmonella tvohimurium, with or without activation, and did not increase the frequency of chromatid gaps, chromatid breaks, or total chromatid aberrations in rat liver cells (Thorpe 1982). 2-Butanone did not cause gene mutations in Saccharomvces cerevisiae (Thorpe 1982), but cause mitotic chromosome loss (Whittaker et al. 1990; Zimmermann et al. 1989) and aneuploidy in S. cerevisiae (Mayer and Goin 1987) at high concentrations. The positive induction of chromosome loss in the yeast cells was enhanced by coexposure to 2-butanone, ethyl acetate, and propionitrile (Zimmermann et al. 1989). The positive induction of aneuploidy was enhanced by coexposure to 2-butanone and nocodazole (Mayer and Goin 1987). It appears, therefore, that 2-butanone alone is not genotoxic to humans.

Cancer. Two retrospective epidemiological studies of industrial workers chronically exposed to 2-butanone in dewaxing plants reported that deaths due to cancer were less than expected (Alderson and Rattan 1980; Wen et al. 1985).

No other studies were located regarding cancer in humans or animals following inhalation exposure to 2-butanone.

TABLE 2-4. Genotoxicity of 2-Butanone *In Vivo* and *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
In vivo:				
Mouse	Micronucleated erythrocytes	Not applicable	-	O'Donoghue et al. 1988
Hamster	Micronucleated erythrocytes	Not applicable	-	Basler 1986
In vitro:				
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	-	-	Thorpe 1982
S. typhimurium	Gene mutation	-	-	O'Donoghue et al. 1988
Escherichia coli	Gene mutation	-	-	Thorpe 1982
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisae	Gene mutation	-	-	Thorpe 1982
S. cerevisiae	Mitotic chromosome loss	No data	+	Whittaker et al. 1990; Zimmerman et al. 1989
S. cerevisiae	Aneuploidy	No data	+	Mayer and Goin 1987
Mammalian cells:				
Rat liver cells (RL_4)	Chromosomal aberrations	No data	-	Thorpe 1982
Rat hepatocytes	Unscheduled DNA synthesis	No data	-	O'Donoghue et al. 1988
BALB/3T3	Morphological transformation	No data	-	O'Donoghue et al. 1988
Mouse lymphoma	Gene mutation	-	-	O'Donoghue et al. 1988

- = negative result; + = positive results

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 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-butanone are discussed in Section 2.5.1.

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

Inhalation exposure to 2-butanone correlates well with blood, breath, and urinary concentrations of unchanged 2-butanone (Brown et al. 1986; Brugnone et al. 1983; Ghittori et al. 1987; Miyasaka et al. 1982). Personal dosimetry was used to measure exposure to 2-butanone among 62 printing plant workers(Miyasaka et al. 1982) and 659 workers in plastic boat, chemical, plastic button, paint, and shoe factories (Ghittori et al. 1987). The correlation between exposure levels and urinary concentration of unchanged 2-butanone was strong in each study (r=O.774 and r=0.91, respectively). Miyasaka et al. 1982) concluded, however, that estimating exposure from urinary levels was reliable on a group basis but not an individual basis. Blood and breath levels of 2-butanone were significantly correlated (r=0.78, p<O.OOl) in volunteers exposed to 200 ppm 2-butanone for 4 hours (Brown et al. 1986). A significant correlation between workroom and urinary 2-butanone concentrations was observed in shoe factory workers (r=0.6877, p<O.OOl) (Brugnone et al. 1983). In the same study, a more significant correlation was observed between workroom concentrations and a 2-butanone urinary metabolite, 3-hydroxy-2-butanone (r=0.8179, p<O.OOl). Another 2-butanone metabolite, 2,3-butanediol, has also been identified in the urine of humans (Liira et al. 1988a, 1988b). No studies were located regarding the correlation between exposure to 2-butanone and urinary levels of the metabolite, 2,3-butanediol. A third metabolite, 2-butanol, was identified in guinea pig-blood; however, no attempt was made to correlate 2-butanol blood levels with exposure to 2-butanone (DiVincenzo et al. 1976). Metabolism of alcohols, hydrocarbons, and other ketones may also yield 2-butanone, 3-hydroxy-2-butanone, and 2,3-butanediol (Dietz and Traiger 1979; Tsukamoto et al. 1985a); therefore, these compounds may confound assessment of exposure to 2-butanone.

Measurements of tissue, blood, and excreta levels may not be an accurate indication of past exposure to 2-butanone. Accumulation in target tissues does not occur because tissue/blood solubility ratios are all near unity; therefore, 2-butanone will not concentrate in specific tissues (Perbellini et al. 1984). The serum half-life of 2-butanone in humans is very short;estimates range from 49 to 96 minutes (Liira et al. 1988a; Lowry 1987). Furthermore, 2-butanone was not detectable in blood or breath measurements reported the morning after a 4-hour exposure to 200 ppm (Brown et al. 1987).

No quantifiable effects that could be used as biomarkers of exposure to 2-butanone were identified.

2.5.2 Biomarkers Used to Characterize Effects Caused by 2-Butanone

2-Butanone induces hepatic microsomal enzymes in rats after oral exposure(Brady et al. 1989; Raunio et al. 1990, Robertson et al. 1989; Traiger et al. 1989), but this enzyme induction has not been associated with more severe liver effects. No other subtle biochemical effects of 2 butanone have been

identified that would be useful as biomarkers to characterize effects of 2-butanone.

2.6 INTERACTIONS WITH OTHER CHEMICALS

The neurological and hepatic effects of 2-butanone alone are minimal. For certain applications, 2-butanone is combined with other chemicals that have serious neurotoxic or hepatotoxic effects. Clinical reports and animal studies have clearly shown that 2-butanone potentiates both the neurotoxicity of ethanol, n-hexane, and methyl-n-butyl ketone and the hepatotoxicity of carbon tetrachloride and chloroform.

Altenkirch et al. (1977) investigated a large outbreak of toxic polyneuropathies in a group of West Berlin "glue sniffers." The development of neuropathies (muscular atrophy, paresthesia, paresis, quadriplegia) coincided with a change in the composition of a glue that was popular for sniffing. Until the fall of 1975, the major constituents of the glue were n-hexane, toluene, ethyl acetate, and benzene. At this time, 2-butanone was added to the mixture and the sudden appearance of the toxic neuropathies began.

A 39-year-old woman who had worked for several years gluing shoes developed polyneuropathy after a few weeks of work in a poorly ventilated shop (Vallat et al. 1981). The glue she was using contained 20% 2-butanone and 8% n-hexane.

"Glue sniffing neuropathy" was also described in a clinical case report of three men who had similar symptoms (King et al. 1985). All had been sniffing the same brand of glue containing light, volatile hydrocarbons(Ce-C,), toluene, and 2-butanone. P-Butanone had recently been added to the glue formulation, and the authors suggested that this may have increased the neurotoxicity. A change in the formulation of a *solvent* compound also precipitated a sudden outbreak of peripheral neuropathy in a coated fabrics plant (Allen et al. 1975; Billmaier et al. 1974). Methyl-n-butyl ketone introduced into a solvent used at the plant was implicated as the causative agent; however, the solvent also contained high concentrations of 2-butanone. Combined exposure to 2-butanone and methyl-n-butyl ketone has not been studied meepidemiologically in humans; therefore, whether P-butanone potentiates methyl-n-butyl ketone neurotoxicity in humans is not known (Katz 1985).

The potentiation of the neurotoxicity of n-hexane and methyl-n-butyl ketone by 2-butanone is well-documented in animals (Altenkirch et al. 1978a, 1978b, 1982a, 1982b; Saida et al. 1976; Takeuchi et al. 1983). Altenkirch et al. (1978a) exposed rats to either 10,000 ppm n-hexane or a combination of 1,000 ppm 2-butanone and 9,000 ppm n-hexane. A summary of three experiments under these conditions showed that rats exposed to the combination of n-hexane and 2-butanone developed paresis more rapidly and in greater numbers than rats exposed to n-hexane only. In the same study, rats exposed to 6,000 ppm

2-butanone only showed no signs of neurotoxicity up to 7 weeks, when all the rats in this group died suddenly of bronchopneumonia. These results were confirmed in a second study; mixtures of 500 ppm n-hexane and 2-butanone (4:1 or 3:2) or 700 ppm (5:2) caused clinical signs of neuropathy 1-5 weeks earlier than 500 ppm n-hexane alone (Altenkirch et al. 1982a). Histological examination revealed morphological changes in the rats similar to those found in youths suffering from glue sniffing neuropathy, including paranodal axon swelling, accumulation of neurofilaments in the cytoplasm, and demyelination. Takeuchi et al. (1983) observed a significant decrease in motor nerve conduction velocity in rats exposed to 300 ppm n-hexane:2-butanone (1:2). In this study, motor nerve conduction velocity increased in rats exposed to 200 ppm 2-butanone alone and did not change in rats exposed to 100 ppm n-hexane alone. Male Wistar rats exposed to n-hexane or a combination of n-hexane and 2-butanone developed ultrastructural changes in the intrapulmonary nerves characteristic of hexacarbon neurotoxicity (Schmidt et al. 1984). Concomitant exposure to n-hexane and 2-butanone decreased the onset of observable neuropathological changes.

Saida et al. (1976) reported a marked potentiation of peripheral neurotoxicity when rats were exposed to methyl-n-butyl ketone:2-butanone (225:1,125 ppm). Rats exposed to methyl-n-butyl ketone only developed paralysis by 66 days. The combination caused paralysis in 25 *days,* while 2-butanone alone had no effect up to 5 months. Histological examination of neurons revealed morphological changes similar to those reported by Altenkirch et al. (1982a), which included paranodal axon swelling, accumulation of neurofilaments, and demyelination. Subcutaneous injection of methyl-n-butyl ketone with or without 2-butanone increased distal motor latency and decreased motor fiber conduction velocity in male Donryu strain rats (Misumi and Nagano 1985). The combination of the two ketones enhanced these effects.

In vitro studies support the hypothesis that 2-butanone potentiates n-hexane and methyl-n-butyl ketone neurotoxicity. Veronesi et al. (1984)observed that, in tissues cultured from fetal mouse spinal cord, dorsal root ganglia, and muscle, the combination of 2-butanone and n-hexane produced giant axonal swellings more rapidly than cultures treated with n-hexane alone. Furthermore, cultures exposed to nontoxic concentrations of n-hexane also developed giant axonal swellings when 2-butanone was administered concomitantly.

Biotransformation of both n-hexane and methyl-n-butyl ketone can produce 2,5-hexanedione (Couri et al. 1978; DiVincenzo et al. 1976; Robertson et al. 1989). This compound is the most potent neurotoxic metabolite of n-hexane and methyl-n-butyl ketone known (Katz 1985). 2-Butanone may potentiate n-hexane and methyl-n-butyl ketone neurotoxicity by enhancing their metabolic conversion to 2,5-hexanedione. Combined administration of methyl-n-butyl ketone and 2-butanone produced more 2,5-hexanedione than administration of methyl-n-butyl ketone alone (Couri et al. 1978). The concentrations of the n-hexane metabolites 2,5-hexanedione and 2,5-dimethylfuran were significantly

higher in the blood and sciatic nerve of rats pretreated by gavage with 2-butanone followed by inhalation exposure to n-hexane compared with rats exposed to n-hexane alone (Robertson et al. 1989). In addition, concomitant oral administration of 2-butanone and 2,5-hexanedione in rats reduced blood 2,5-hexanedione clearance (Ralston et al. 1985).

Ethyl-n-butyl ketone is a weak neurotoxin (O'Donoghue et al. 1984). Oral administration in rats for several weeks caused the paranodal axon swelling and neurofilamentous hyperplasia characteristic of n-hexane and methyl-n-butyl ketone neurotoxicity. Biotransformation of ethyl-n-butyl ketone produced two neurotoxic metabolites, 2,5-hexanedione and 2,5-heptanedione. 2,5-Heptanedione can be further metabolized to 2,5 hexanedione. Concomitant inhalation exposure to 700 ppm ethyl-n-butyl ketone and 700 ppm 2-butanone for 4 consecutive days caused a 2.6-fold increase in the serum concentration of 2,5-heptanedione. Oral administration of 2-butanone potentiated the development of clinical and histological signs of ethyl-n-butyl neurotoxicity.

2-Butanone has also been found to potentiate the neurotoxicity of ethanol (Cunningham et al, 1989). Mice pretreated intraperitoneally with 2-butanone followed by intraperitoneal injection of ethanol 30 minutes later showed prolonged loss of righting reflex induced by ethanol. 2-Butanone also decreased the rate of ethanol elimination in mice *in vivo* and inhibited the in vitro activity of alcohol dehydrogenase, the main mechanism for ethanol elimination. These results suggest that 2-butanone potentiated the neurotoxicity of-ethanol by inhibiting its metabolism by alcohol dehydrogenase.

2-Butanone is not a universal potentiator of hydrocarbon- and aliphatic ketone-induced neuropathies (O'Donoghue et al. 1982). Concomitant oral administration of 2-butanone and 5-nonanone did not potentiate the neurotoxicity of 5-nonanone.

2-Butanone alone is minimally neurotoxic (Altenkirch et al. 1978a; Saida et al. 1976). This compound, however, is frequently mixed with n-hexane and methyl-n-butyl ketone for various commercial and industrial applications. The previous discussion emphasizes the public health hazard of mixed solvent exposure to 2-butanone. Exposure to a mixed solvent is more likely to occur in an occupational setting or at a hazardous waste site, than exposure to 2-butanone alone.

2-Butanone alone is not highly hepatotoxic (see the discussion of Hepatic Effects in Section 2.2.1.2) but has a well-documented role in potentiating haloalkane-induced hepatotoxicity (Brown and Hewitt 1984; Dietz and Traiger 1979; Hewitt et al. 1983, 1986, 1987; Tanii et al. 1986). Intraperitoneal injection of chloroform (0.5 mL/kg) caused a nine-fold increase in rat SGPT activity (Brown and Hewitt 1984). In contrast, chloroform injection caused a 195-fold increase in rat SGPT activity if administered 18 hours after oral administration of 2-butanone. Similarly, intraperitoneal injection of

chloroform increased rat plasma ornithine carbamyl transferase activity 215-fold if given 18 hours after oral administration of 2-butanone (Hewitt et al. 1983). In addition to the doses administered, the length of time between administration of 2-butanone and the chloroform injection determined the severity of hepatotoxicity (Hewittet al. 1987). Measurements of SGPT and plasma ornithine carbamyl transferase revealed that 2-butanone is most efficacious for potentiation of chloroform-induced hepatotoxicity if administered 18 hours before chloroform.

2-Butanone also potentiates carbon tetrachloride-induced hepatotoxicity (Dietz and Traiger 1979; Traiger et al, 1989). Measurement of SGPT activity and hepatic triglyceride content showed that administration of 2-butanone 16 hours before intraperitoneal injection of carbon tetrachloride significantly enhanced liver damage. The mechanism of P-butanone potentiation of chloroform and carbon tetrachloride hepatotoxicity may be related to biotransformation of the ketone to its metabolite, 2,3-butanediol. Carbon tetrachloride increased rat SGPT 164-fold when injected 16 hours after oral administration of 2,3-butanediol. Replacement of 2,3-butanediol with 2-butanone increased the transaminase 66-fold. Hepatic triglyceride content was potentiated to a similar degree by both 2-butanone and 2,3-butanediol. However, the maximal potentiation of carbon tetrachloride-induced hepatic injury by pretreatment with 2-butanone coincided with increased microsomal enzyme activity within the same time frame following exposure to 2-butanone alone (Traiger et al. 1989). This strongly suggests that 2-butanone potentiates the hepatotoxicity of carbon tetrachloride by enhancing its metabolism to toxic intermediates. The mechanism of 2-butanone potentiation of chloroform-induced hepatotoxicity apparently does not involve biotransformation of chloroform to a reactive intermediate, an alteration of the cytochrome P-450 system, or depletion of liver glutathione (Hewitt et al. 1987). It is possible that 2,3-butanediol also contributes to the toxicity of chloroform.

Pretreatment of ddY mice with carbon tetrachloride 24 hours before oral administration of 2-butanone reduced the 2-butanone LD,, about 20% (Tanii et al. 1986). The mechanism of this effect was not investigated.

Exposure of pregnant rats continuously to n-hexane alone (l,OOO-1,500 ppm) or n-hexane and 2-butanone (1,200 ppm n-hexane, 300 ppm 2-butanone) throughout gestation and/or during the postnatal period resulted in reduced birth weight of pups, and weight gain reduction persisted during the postnatal exposure period (Stoltenburg-Didinger et al. 1990). The effect was more pronounced with the mixture of solvents. In addition, hindlimb weakness in one dam during the gestational exposure period progressing to quadriplegia in all dams during the postpartum exposure period was for the solvent mixture, while only hindlimb weakness was observed in the dams exposed observed n-hexane alone.

Coexposure of S. cerevisiae to 2-butanone, ethyl acetate, and propionitrile enhanced the induction of chromosome loss caused by 2-butanone (Zimmermann et al. 1989). Coexposure of S. cerevisiae to 2-butanone and nocodazole enhanced the induction of aneuploidy caused by 2-butanone alone (Mayer and Goin 1987).

2.7 POPULATIONS THAT ABE UNUSUALLY SUSCEPTIBIE

No studies were located that identified populations that are unusually susceptible to adverse health effects after exposure to 2-butanone. The very young and the very old are typically more susceptible to chemical, toxicity than are older children, adolescents, and healthy adults. Individuals that are alcoholics and those with existing liver disease would be expected to metabolize 2-butanone differently than the general population. Persons with existing neuropathies may also be more susceptible. Exposure to both 2-butanone and n-hexane or methyl-n-butyl ketone is possible in occupational settings and at hazardous waste sites; thus, neurological effects of n-hexane and methyl-n-butyl ketone may be greater with coexposure to 2-butanone. Likewise, occupational exposure or exposure at hazardous waste sites to a combination of 2-butanone and the haloalkanes, carbon tetrachloride, or chloroform, presents a greater risk for liver damage.

2.8 MITIGATION OF EFFECTS

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

2-Butanone has a low order of systemic toxicity. The main effects in humans are irritation of respiratory tissues and eyes and nonspecific neurological effects, such as headache, dizziness, nausea, and fatigue. Such effects are characteristic of solvent exposure and are mitigated primarily by removing affected individuals from exposure conditions and decontaminating exposed areas (Bronstein and Currance 1988; Stutz and Janusz 1988). For example, contaminated clothing is removed and skin washed. If the eyes were exposed, they are flushed with water. For ingestion of 2-butanone, there is controversy as to whether or not to administer emetics. The controversy centers around the risk of aspiration of vomitus into the lungs during emesis. Administration of activated charcoal has been suggested to reduce gastrointestinal absorption. Please refer to Bronstein and Currance (1988) and Stutz and Janusz (1988) for more complete information.

Although 2-butanone alone is not highly neurotoxic or hepatotoxic, it potentiates the neurotoxicity of n-hexane and methyl-n-butyl ketone, and the hepatotoxicity of chloroform and carbon tetrachloride (see Section 2.6). Exposure to 2-butanone with other solvents is more likely than exposure to 2-butanone alone in occupational and environmental settings. Since both n-hexane and methyl-n-butyl ketone can be

metabolized to 2,5-hexanedione (Couri et al. 1978; DiVincenzo et al 1976), a potent neurotoxic agent (Katz 1985), 2-butanone may potentiate the neurotoxicity of the other chemicals by enhancing the biotransformation of n-hexane and methyl-n-butyl ketone to 2,5-hexanedione by inducing microsomal enzymes. The potentiation of the hepatotoxicity of carbon tetrachloride and chloroform by 2-butanone may be related to the biotransformation of 2-butanone to 2,3-butanediol, a metabolite that potentiates the hepatotoxicity of carbon tetrachloride to a greater extent than does 2-butanone (Dietz and Traiger 1979). Alternatively, the induction of microsomal enzymes by 2-butanone may enhance the biotransformation of chloroform and carbon tetrachloride to toxic intermediates (Brady et al. 1989; Traiger et al. 1989). If carbon tetrachloride or chloroform shift metabolic pathways of 2-butanone in favor of greater formation of 2,3-butanediol, administration of an agent that blocks this shift could mitigate the potentiation. 2-Butanone is reduced to 2-butanol and oxidized to 3-hydroxy-2-butanone, which is further reduced to 2,3-butanediol(DiVincenzo et al. 1976). However, the enzyme systems involved in the biotransformation of 2-butanone have not been characterized. Similarly, if 2-butanone enhances the metabolism of chloroform and carbon tetrachloride by inducing microsomal enzymes, agents that block this induction could mitigate this potentiation.

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-butanone is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 2-butanone.

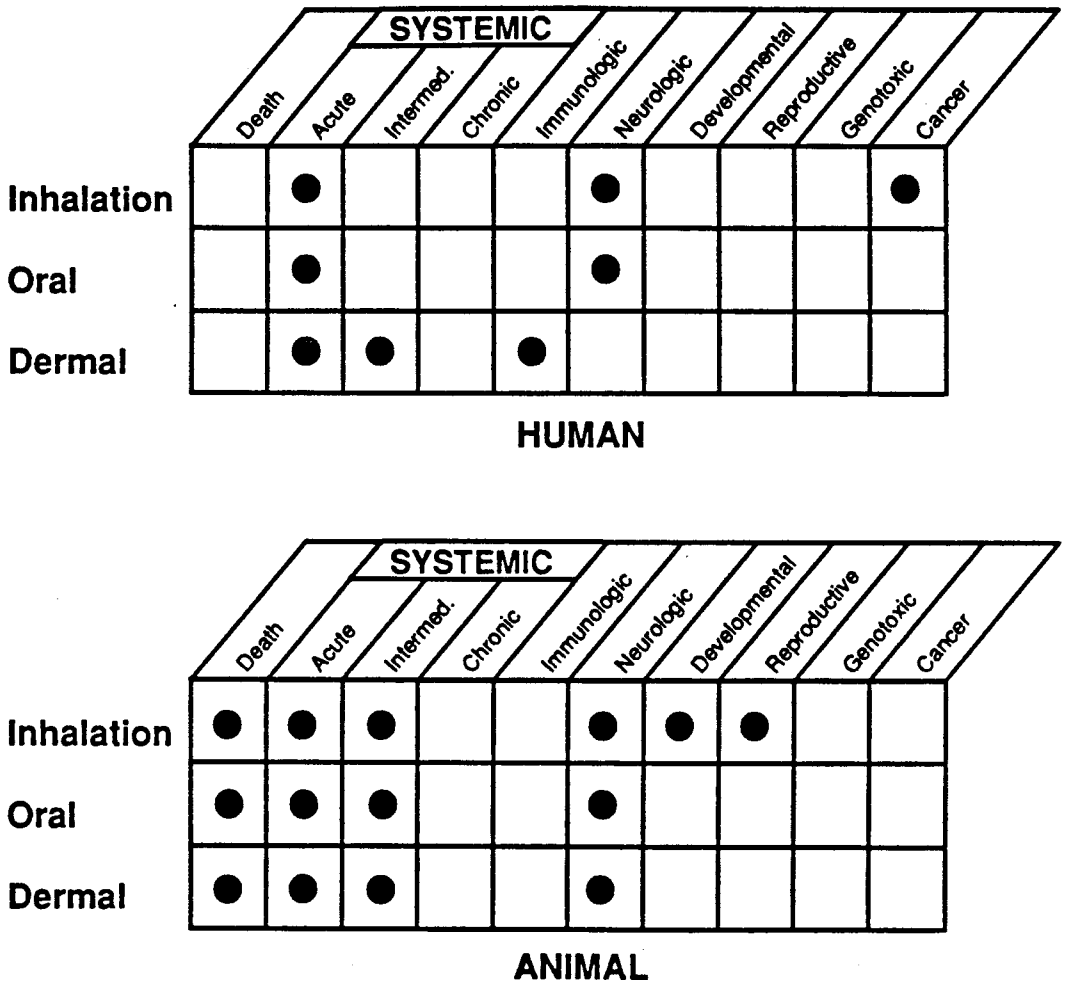
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data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

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 2-butanone are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of 2-butanone. 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.

Studies regarding the adverse health effects of exposure to 2-butanone in humans is limited (Figure 2-4). No reports exist regarding death in humans

FIGURE 2-4. Existing Information on Health Effects of 2-Butanone



● Existing Studies

following exposure to 2-butanone by any route. Existing information regarding systemic effects of 2-butanone exposure have come primarily from two clinical reports involving accidental poisoning: one by oral exposure and one by inhalation (Berg 1971; Kopelman and Kalfayan 1983). A clinical study reported contact urticaria triggered by dermal -exposure to 2 butanone in a 48-year-old male painter (Varigos and Nurse 1986). Intermediate dermal exposure to 2-butanone had no effect on humans (Wahlberg 1984). Acute inhalation studies in humans showed no adverse neurological effects (Dick et al. 1984, 1988, 1989). However, 2-butanone produced nose, throat, and eye irritation in humans (Nelson et al. 1943). Epidemiological studies showed no clear relationship between occupational exposure to 2-butanone and the development of neoplasms (Alderson and Rattan 1980; Wen et al. 1985).

Animal studies regarding death after acute and intermediate exposure to 2-butanone by inhalation, oral, dermal, and other routes are available. Several studies are also available that show that acute and intermediate inhalation exposures have minimal or no systemic effects. Minimal effects were limited to small increases in organ weight (Cavender et al. 1983; Toftgard et al. 1981). Inhalation, oral, and dermal studies showed that 2-butanone is minimally neurotoxic in most species. Guinea pigs exposed acutely to high concentrations (10,000 ppm) developed incoordination and narcosis (Patty et al 1935). Juvenile baboons exposed to 100 ppm 2 butanone also appeared to show early signs of incoordination and narcosis in a complex discriminant neurobehavioral test (Geller et al. 1979). Histological examination of reproductive organs of male and female rats exposed by inhalation to 5,000 ppm revealed no effects (Cavender and Casey 1981; Cavender et al. 1983). Studies of acute oral exposure showed that 2-butanone caused renal tubular necrosis (Brown and Hewitt 1984; Hewitt et al. 1983) and induced hepatic microsomal enzymes (Brady et al. 1989; Raunio et al. 1990, Robertson et al. 1989; Traiger et al. 1989). One intermediate oral exposure showed that 2-butanone was not neurotoxic (Ralston et al, 1985). Acute and intermediate dermal exposures to 2-butanone were mildly irritating to the skin of rabbits, rats, and guinea pigs (Hazleton Laboratories 1963a; Wahlberg 1984). No reports of systemic toxicity are available for dermal exposure. Several studies demonstrating that 2-butanone is moderately irritating to the eyes of rabbits are available. 2-Butanone was fetotoxic, causing delayed development in fetuses of rats (Deacon et al. 1981; Schwetz et al. 1974) and mice (Mast et al. 1989) exposed by inhalation.

Several studies are available regarding 2-butanone potentiation of n-hexane and methyl-n-butyl ketone neurotoxicity and 2-butanone potentiation of haloalkane hepatotoxicity.

2.9.2 Data Needs

Acute-Duration Exposure. Several studies are available that report the results of acute duration exposure to 2-butanone by inhalation, oral, and dermal routes in both humans and animals. In acute inhalation studies, an

LC_{50} value in rats (LaBelle and Brieger 1955) and other exposures that caused death in rats (Klemisch 1988; Smyth et al. 1962), mice (LaBelle and Brieger 1955), and guinea pigs (Patty et al. 1935) were identified. The target organs identified in guinea pigs after acute inhalation exposure to high concentrations of 2-butanone are the respiratory system, liver, kidney, eye, and central nervous system Patty et al. 1935. Slight neurotoxicity was also seen in mice and baboons exposed to low concentrations (DeCeaurriz et al. 1983; Geller et al. 1979). Narcosis and incoordination were observed in guinea pigs exposed acutely to high concentrations of 2-butanone (Patty et al. 1935). An acute-duration inhalation MRL was not derived because target organs of rats and mice have not been sufficiently investigated. Although target organs of acute inhalation exposure of rats and mice have not been sufficiently investigated, intermediate duration studies indicate that effects on the liver, kidney, respiratory system, and nervous system of rats are minimal. In acute oral studies, LD_{50} values for rats (Kimura et al. 1971; Smyth et al. 1962) and mice (Tanii et al. 1986) were available, and the kidney was identified as a target (Brown and Hewitt 1984). No acute oral MRL was derived because target organs have not been sufficiently investigated. Furthermore, inhalation studies indicate that 2-butanone is a developmental toxicant, but developmental effects after oral exposure were not studied. Acute dermal studies have shown that 2-butanone is a skin and eye irritant in rabbits (Hazleton Laboratories 1963a, 1963b) and guinea pigs (Anderson et al. 1986; Wahlberg 1984), but the systemic toxicity of acute dermal exposure has not been investigated. The available pharmacokinetic data are not sufficient to predict whether target organs would be similar by the various routes of exposure. Acute exposure of humans near a toxic waste site to 2-butanone alone would probably not have serious clinical consequences. 2-Butanone is detectable by humans at concentrations far below its OSHA and NIOSH permissible levels because of its odor. Further acute exposure studies with 2-butanone alone would probably not be useful. In contrast, further acute exposure studies by oral, inhalation, and dermal routes of 2-butanone combined with such hepatotoxins as chloroform and carbon tetrachloride, or with such neurotoxins as n-hexane and methyl-n-butyl ketone would yield valuable information on the potentiation of the hepatotoxicity and neurotoxicity, resperhively, of the other-chemicals by 2-butanone. These chemicals are often found together in formulations used occupationally and they might be stored together at toxic waste sites. Therefore, workers and populations surrounding hazardous waste sites might be exposed to these substances for acute durations.

Intermediate-Duration Exposure. A comprehensive 90-day inhalation study in rats showed that 2-butanone did not have adverse effects in the respiratory, cardiovascular, gastrointestinal, musculoskeletal, hematological, hepatic, renal, or dermal/ocular systems (Cavender and Casey 1981; Cavender et al. 1983). The most serious effect was slightly increased liver weight at the highest concentration tested, 5,000 ppm. Occupational exposures to concentrations this high are unlikely since humans find 350 ppm 2-butanone intolerable (Nelson et al. 1943). No signs of neurotoxicity, either clinical

or histological, were observed in several studies of intermediate exposures to high concentrations of 2-butanone up to 6,000 ppm (Altenkirch et al. 1978a, 1978b; Cavender and Casey 1981; Cavender et al. 1983). Therefore, most organs and tissues in humans probably would not be adversely affected by intermediate 2-butanone exposures either occupationally or near toxic waste sites. An intermediate duration inhalation MRL was not derived because nose and throat irritation occurred in humans at acute inhalation exposure levels lower than the NOAEL values for intermediate duration inhalation exposure in animals. No intermediate oral or dermal studies investigated the systemic toxicity of 2-butanone by these routes, and the available pharmacokinetic data are not. Sufficient to predict whether target organs would be similar by the various routes of exposure. 2-Butanone has been detected in air, water, food, and soil (see Section 5.4); therefore, exposures by the inhalation, oral, and dermal routes are possible. From a public health perspective, exposure to solvent mixtures is more likely than exposure to a single pure chemical. Therefore, intermediate exposure studies of 2-butanone mixed with other solvents (hexacarbons and haloalkanes), the toxicity of which is potentiated by 2-butanone, would provide valuable information on neurotoxicity and systemic toxicity. This information is important since these chemicals are often found together in solvents used occupationally, and they might be stored together at hazardous waste sites where surrounding populations could be exposed for intermediate durations.

Chronic-Duration Exposure and Cancer. No studies were located regarding the health effects of chronic exposure to 2-butanone by any route in humans or animals, but acute and intermediate duration inhalation studies indicated that by itself, 2-butanone is minimally toxic. Pharmacokinetic data are insufficient to predict the possible target organs of chronic exposure by any route. Since 2-butanone has been detected in air, water, food, and soil (see Section 5.4), exposures by the inhalation, oral, and dermal routes are possible. 2-Butanone is often found in formulations with other chemicals, such as chloroform, carbon tetrachloride, n-hexane, and methyl-n-butyl ketone, the toxicities of which -2-butanone potentiates. These chemicals may be stored together at hazardous waste sites. Chronic inhalation, oral, and dermal studies in which animals are administered these chemicals in combination with 2-butanone may provide dose-response information for the potentiation of the neurotoxicity and hepatotoxicity of these chemicals by 2-butanone. This information is important because there are populations surrounding hazardous waste sites that might by exposed to these chemicals for similar durations.

Although no cancer bioassays were available, preliminary epidemiological studies suggest that occupational exposure to 2-butanone does not increase the development of neoplasms. Furthermore, 2-butanone was not genotoxic, either with or without metabolic activation, in several microorganisms and cultured mammalian cells (O'Donoghue et al. 1988; Thorpe 1982). Furthermore, no induction of micronuclei was found in the erythrocytes of hamsters (Basler 1986) or mice (O'Donoghue et al. 1988) after intraperitoneal injection with

2-butanone. On the basis of this information, 2-butanone does not appear to be carcinogenic.

Genotoxicity. No induction of micronuclei was found in the erythrocytes of hamsters (Basler 1986) or mice (O'Donoghue et al. 1988) after intraperitoneal injection with 2-butanone. A comprehensive battery of in vitro tests showed that 2-butanone was not mutagenic in two prokaryotic organisms and two eukaryotic organisms, did not transform mammalian cells in culture, and did not induce unscheduled DNA synthesis in rat primary hepatocytes (O'Donoghue et al. 1988; Thorpe 1982). 2-Butanone did not cause gene mutations in S. cerevisiae (Thorpe 1982), but caused mitotic chromosome loss (Whittaker et al. 1990; Zimmermann et al. 1989) and aneuploidy in S. cerevisiae (Mayer and Goin 1987) at high concentrations. The positive induction of chromosome loss in the yeast cells was enhanced by coexposure to 2-butanone, ethyl acetate, and propionitrile (Zimmermann et al. 1989). The positive induction of aneuploidy was enhanced by coexposure to 2-butanone and nocodazole (Mayer and Goin 1987). Although 2-butanone contains an electrophilic center at the carbonyl carbon, further testing for genotoxicity does not seem warranted, except in combination with other solvents.

Reproductive Toxicity. No studies were located regarding effects on reproductive capacity or reproductive organs and tissues in humans following exposure to 2-butanone. The authors of a health hazard evaluation report for NIOSH concluded that a perceived increase in the number of spontaneous abortions among female workers believed to result from exposure to 2-butanone and several other volatile chemicals at a shoe factory was not related to exposure (Tharr et al. 1982). No histopathological lesions were found in male or female reproductive organs of rats exposed to 5,000 ppm 2-butanone for 90 days (Cavender and Casey 1981; Cavender et al. 1983), but reproductive function was not assessed. Further studies of the reproductive function of 2-butanone by all durations and routes would provide valuable information particularly if the studies include histological examination of the organs and tissues of the reproductive. system. If reproductive organs were identified as targets of 2-butanone toxicity, single or multigeneration reproductive studies probably would be warranted. Since 2-butanone potentiates the neurotoxicity or hepatotoxicity of certain chemicals, it would be valuable to investigate the reproductive effects of mixed solvent exposures that include 2-butanone. This investigation would be useful because 2-butanone is often found in mixtures of other solvents in occupational settings, and these mixtures may be found together at or near hazardous waste sites.

Developmental Toxicity. Information regarding developmental toxicity of 2-butanone in humans was not located. 2-Butanone was slightly fetotoxic in rats (Deacon et al. 1981; Schwetz et al. 1979) and mice (Mast et al. 1989)following inhalation exposure of pregnant rats and mice to 3,000 ppm. The fetotoxicity was related to delayed development. Furthermore, five of eight pregnant rats exposed continuously to 800 ppm throughout gestation failed to deliver litters (Stoltenburg-Didinger et al. 1990). In addition,

developmental effects were more pronounced in pups born to rat dams exposed to a mixture of n-hexane and 2-butanone than in pups born to dams exposed to n-hexane alone (Stoltenburg-Didinger et al. 1990). This study, however, was very poorly reported, with very little information provided on exposure to 2-butanone alone. No developmental or distribution studies have been conducted by the oral route, but there is no reason to believe that 2-butanone or its metabolites could not cross the placenta after administration by the oral route. Therefore, it is likely that orally administered 2-butanone would be fetotoxic in these species. Determination of the doses needed to produce the fetotoxicity by the oral route would provide valuable information. Since 2-butanone potentiates the neurotoxicity or hepatotoxicity of certain chemicals, it would be valuable to further investigage the developmental effects of mixed solvent exposures that include 2-butanone. Such a study would be useful because 2-butanone is often found in mixtures with other solvents in occupational settings, and these mixtures may be fould at or near hazardous waste sites.

Immunotoxicity. No studies were located regarding immunotoxicity after oral exposure to 2-butanone. A clinical report of contact urticaria in a 47-year-old painter exposed occupationally to 2-butanone (Varigos and Nurse 1986) suggests that skin sensitivity requires more study. Altenkirch et al. (1978a) reported that 19/19 rats died suddenly of pathologically confirmed bronchopneumonia after 7 weeks of inhalation exposure to 6,000 ppm 2-butanone. 2-butanone may weaken the immune system, thus predisposing humans and animals to infection. No histopathological lesions were found in the thymus, lymph nodes, spleen, or bone marrow of rats exposed to 5,000 ppm or less of 2-butanone for 90 days (Cavender and Casey 1981; Cavender et al. 1983), but tests for immune function were not performed. Therefore, a study of the effects of 2-butanone on immune function (thymus, lymph nodes, peripheral blood lymphocytes, etc.)would provide valuable information regarding the immunotoxicity of 2-butanone.

Neurotoxicity. 2-butanone was not neurotoxic at a concentration of 200 ppm in several acute inhalation exposure studies in humans (Dick et al. 1984, 1988, 1989). Neurobehavioral effects have been observed in mice (1,602 ppm))DeCeaurriz et al. 1983) and baboons (100 ppm) (Geller et al. 1979) exposed acutely by inhalation. Guinea pigs displayed narcosis and incoordination after acute inhalation exposure to high concentrations (Patty et al. 1935). Clinical signs of neurotoxicity were also observed in rats treated acutely by gavage with a high dose of 2-butanone (Stillmeadow Inc. 1978). However, 2-butanone is not generally regarded as being highly neurotoxic when administred alone. In acute and intermediate exposure studies in animals, it markedly potentiated the neurotoxicity of n-hexane and methyl-n-butyl ketone both in humans and animals. A comprehensive study of acute, intermdiate, and chronic exposures to mixtures of 2-butanone, n-hexane, and methyl-n-butyl ketone by inhalation, oral, and dermal routes will provide valuable information regarding the neurotoxicity of these compounds. Such a study would be particularly valuable because 2-butanone is

often found occupationally in mixtures containing n-hexane and methyl-n-butyl ketone, and these chemicals would probably be found together at hazardous waste sites.

Epidemiological and Human Dosimetry Studies. One study with humans etermined that inhalation exposure to 100 ppm for 15 minutes was irritating to the nose and throat, and exposure to 350 ppm was intolerable (Nelson et al. 1943). In three separate studies, volunteers exposed to 200 ppm had no neurobehavioral effects (Dick et al. 1984, 1988, 1989). Two epidemiological studies of chemical company workers exposed to 2-butanone showed inconclusive results regarding increased risk of cancer (Alderson and Rattan 1980; Wen et al. 1985). No epidemiological studies regarding other health effects of 2-butanone exposure were located. Therefore, valuable epidemiological information could be obtained from further studies of cancer and other health effects, particularly neurotoxicity and reproductive and developmental toxicity.

Biomarkers of Exposure and Effect. The only known biomarkers of 2-butanone exposure are blood, breath, and urinary concentrations of 2-butanone and its metabolites (Brown et al. 1986; Brugnone et al. 1983; Ghittori et al. 1987; Miyasaka et al. 1982). 2-Butanone is rapidly cleared from the body, and existing studies show that accumulation of 2-butanone in tissues does not occur to a significant extent. Furthermore, 2-butanone alone is relatively free of adverse health effects. Therefore, development of biomarkers of exposure to a battery of solvents often used occupationally in combination with 2-butanone would be more valuable than development of biomarkers for 2-butanone alone.

2-Butanone exposure has no specific effects that can be used as biomarkers for exposure by any route or for any duration of exposure.

Absorption, Distribution, Metabolism, and Excretion. 2-Butanone is absorbed by inhalation (Liira et al. 1988a, 1988b, 1990, 1991) and oral exposure (Brown and Hewitt 1984; Dietz and Traiger 1979; Dietz et al. 1981; Hewitt et al. 1983; Sakata et al. 1989). Net retention of inhaled 2-butanone is approximately 50% in humans (Liira et al. 1988a, 1988b). Studies of absorption after dermal exposure would provide valuable information on this occupationally significant route of entry. Available data regarding the relative rates or extent of absorption, metabolism, distribution, and excretion by the three routes of exposure are not sufficient to draw meaningful conclusions. 2-Butanone is equally soluble in all tissues and organs measured (Perbellini et al. 1984). Therefore, 2-butanone is probably evenly distributed throughout the body. The primary route of excretion appears to be the lungs. The metabolic pathways for 2-butanone have been thoroughly studied in rats (Dietz and Traiger 1979; Dietz et al. 1981) and guinea pigs (DiVincenzo et al. 1976). Similar metabolites have been identified in humans (Liira et al. 1988a, 1988b; Miyasaka et al. 1982). In rats, 30% of an oral dose of 2-butanone was converted to 2,3-butanediol (Dietz

et al. 1981). Potentiation of the neurotoxicity of ethanol, n-hexane, and methyl-n-butyl ketone and the hepatotoxicity of haloalkanes by 2-butanone may involve interactions in the biotransformation of these compounds (Brady et al. 1989; Cunningham et al. 1989; Raunio et al. 1990; Robertson et al. 1989; Traiger et al. 1989). Further studies regarding the interaction of hexacarbons, haloalkanes, and 2-butanone at the metabolic level may provide valuable information.

Comparative Toxicokinetics. Available human data show that 2 butanone is metabolized primarily to 2,3-butanediol and 3-hydroxy-2-butanone, but the extent of metabolism appears to be small (Liira et al. 1988a, 1988b). In an occupational exposure study of 2-butanone, only 3-hydroxy-2-butanone was observed (Brugnone et al. 1983). In rats and guinea pigs, a third metabolite, 2-butanol, was observed (Dietz et al. 1981; DiVincenzo et al. 1976). About 30% of an oral dose of 2-butanone in rats later appeared in plasma as 2,3-butanediol (Dietz et al. 1981). 2-Butanol is also a product of 2-butanone metabolism in humans (Liira et al. 1990). 2-Butanone potentiates the neurotoxicity of n-hexane and methyl-n-butyl ketone and the hepatotoxicity of haloalkanes. The 2-butanone metabolite, 2,3-butanediol, may be more efficacious for potentiating the hepatotoxicity of the haloalkanes than 2-butanone. Therefore, valuable information would be gained by toxicokinetic studies of 2-butanone and its metabolites as they pertain to the toxicity of the hexacarbons and haloalkanes.

Mitigation of Effects. 2-Butanone by itself has a low order of systemic toxicity. However, exposure to 2-butanone with other solvents, which is more likely in occupational and environmental settings than is exposure to 2-butanone alone, results in a potentiation of the neurotoxicity and hepatotoxicity of the other solvents. Further studies that investigate the mechanism by which 2-butanone potentiates the toxicity of other ketones, n-hexane, chloroform, and carbon tetrachloride would be useful in planning research aimed to develop agents that would interfere with the mechanism, thereby mitigating the potentiation.

2.9.3 On-going Studies

No information regarding current studies of the health effects of 2-butanone was located.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

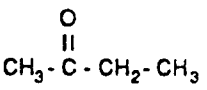
Data pertaining to the chemical identity of 2-butanone are listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of 2-butanone are presented in Table 3-2.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of 2-Butanone

Characteristic	Information	Reference
Chemical name	2-Butanone	CAS 1989
Synonyms	Methyl ethyl ketone; MEK; ethyl methyl ketone; methyl acetone; and others	CAS 1989; SANSS 1989; Chemline 1989
Trade name(s)	Meetco	OHM/TADS 1989
Chemical formula	C_4H_8O	CAS 1989
Chemical structure		
Identification numbers:		
CAS registry	78-93-3	CAS 1989
NIOSH RTECS	EL6475000	HSDB 1989
EPA hazardous waste	U159	HSDB 1989
OHM/TADS	7216796	Chemline 1989
DOT/UN/NA/IMCO	UN1193, UN1232	Chemline 1989
HSDB	99	HSDB 1989
NCI	No data	

CAS = Chemical Abstracts Service
EPA = Environmental Protection Agency
DOT/UN/NA/IMCOP = Department of Transportation/United Nations/North America/ International Maritime Consultive Organization
HSDB = Hazardous Substance Data Bank
NCI = National Cancer Institute
NIOSH = National Institute for Occupational Safety and Health
OHM/TADS = Oil and Hazardous Materials Technical Assistance Data Base
RTECS = Registry of Toxic Effects of Chemical Substances
SANSS = Structure and Nomenclature Search System

TABLE 3-2. Physical and Chemical Properties of 2-Butanone

Property	Information	Reference
Molecular weight	72.11	Weast et al. 1988
Color	Colorless	Sax and Lewis 1987
Physical state	Liquid	Sax and Lewis 1987
Melting point	-86.3°C	Weast et al. 1988
Boiling point	79.6°C	Weast et al. 1988
Density (liquid) at 20°C	0.8054	Weast et al. 1988
Odor	Acetone-like	Sax and Lewis 1987
Odor threshold		
Water	8.4 ppm	Amoore and Hautala 1983
Air	5.4 ppm	Amoore and Hautala 1983
Solubility		
Water at 25°C	136,000 mg/L	Tewari et al. 1982
Organic solvents	Benzene, alcohol, ether, oils, most organic solvents	Sax and Lewis 1987; Neier and Strehlke 1985
Partition coefficient		
Log octanol/water	0.29	Hansch and Leo 1985
Log K_{oc}	0.55	Roy and Griffin 1985
Vapor pressure at 25°C	90.6 mmHg	Riddick et al. 1986
Henry's law constant at 25°C	5.77×10^{-5} atm m^3/mol	Rathburn and Tai 1987
Autoignition temperature	515°C	Sax and Louis 1987
Flashpoint		
Closed cup	-2°C	Riddick et al. 1986
Open cup	1°C	Riddick et al. 1986
Flammability limits in air	2-10%	Sax and Lewis 1987
Conversion factors		
ppm (v/v) to mg/m^3 in air (20°C)	1 ppm = 2.93 mg/m^3	
mg/m^3 to ppm (v/v) in air (20°C)	1 mg/m^3 = 0.341 ppm	
Bioconcentration factor	0.98 (calculated from K_{ow})	Lyman et al. 1982
Explosive limits	No data	

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

According to the most recent edition of U.S. International Trade Commission (USITC 1989), 482,028,000 pounds of 2-butanone were produced in the United States in 1988. The production volume for 1986 and 1987 was 600,440,000 and 671,859,000 pounds, respectively (USITC 1987, 1988). Total U.S. capacity for 1989 has been estimated at 622 million pounds (SRI 1989). Production of 2-butanone has been flat in the past decade, but it is expected to grow at 2%-3% through 1991 (Chemical Marketing Reporter 2987). Current manufacturers of 2-butanone are included in Table 4-1. According to the Toxic Release Inventory (TRI 1989), 2,218 facilities manufacture or process 2-butanone. These facilities had a maximum amount of 2-butanone on site of approximately 1,670,000,000 pounds in 1987. These data are presented in Table 4-2. The quality of the data must be viewed with caution since the 1987 data represent first-time, incomplete reporting by these facilities. Not all facilities that should have reported have done so.

2-Butanone is produced on a commercial scale by one of two processes. The vapor-phase dehydrogenation of set-butanol.(2-butanol), itself obtained from the hydrolysis of butene, accounts for 88% 2-butanone production (Neier and Strehlke 1985; Papa and Sherman 1981). In the other commercially significant process, 2-butanone is obtained as a byproduct of acetic acid production. In this methodology, liquified butane is subjected to catalytic oxidation.

4.2 IMPORT/EXPORT

Approximately 16% of the total U.S. production of 2-butanone is exported to other countries (Chemical Marketing Reporter 1987). Imports into the United States amounted to about 52 million pounds in 1986.

4.3 USE

2-Butanone exhibits outstanding solvent properties, and combined with its low cost, it is often the choice solvent for various coating systems (Neier and Strehlke 1985; Papa and Sherman 1981). Uses of 2-butanone can be broken down into the following categories: coatings solvent, 50%; adhesives, 13%; magnetic tapes, 8%; lube oil dewaxing, 4%; printing inks, 3%; exports, 16%; and miscellaneous, 6% (Chemical Marketing Reporter 1987). Examples of specific applications include its use as a solvent for nitrocellulose, lacquers, rubber cement, printing inks, paint removers, vinyl films, resins, rosins, polystyrene, chlorinated rubber, polyurethane, acrylic coatings, and cleaning solutions (Neier and Strehlke 1985; Papa and Sherman 1981; Sax and Lewis 1987). 2-Butanone is used in the production of synthetic leathers, transparent paper, and aluminum foil. It is also used in the degreasing of metals, as an extraction solvent, in dewaxing applications, and as a solvent for the production of smokeless powders.

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

TABLE 4-1. Current Manufacturers of 2-Butanone[a]

Company	Location
ARCO Chemical Co.	Channelview, TX
Exxon Corporation	Baton Rouge, LA
Hoechst Celanese Corp.	Pampa, TX
Shell Oil Company	Norco, LA
Union Carbide Corp	No data

[a]Derived from SRI 1989; USITC 1989

TABLE 4-2. Facilities That Manufacture or Process 2-Butanone[a]

State[b]	No. of facilities	Range of maximum amounts on site in thousands of pounds[c]	Activities and uses[d]
AL	29 (2)[e]	0.1-999	2, 3, 8, 9, 10, 11, 12, 13
AR	41 (2)[e]	0-999	1, 2, 3, 7, 8, 9, 11, 12, 13
AZ	21 (1)[e]	0.1-99	2, 7, 8, 11, 12, 13
CA	193 (12)[e]	0-9,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
CO	14 (2)[e]	0.1-99	8, 9, 11, 12, 13
CT	37 (1)[e]	0-999	2, 8, 9, 10, 11, 12, 13
DE	10	1-999	3, 8, 11, 12, 13
FL	29 (3)[e]	0-999	2, 3, 4, 7, 8, 10, 11, 12, 13
GA	58 (2)[e]	0-999	2, 3, 4, 7, 8, 9, 10, 11, 12, 13
IA	30 (1)[e]	0-49,999	2, 8, 9, 10, 11, 12, 13
ID	1	1-9	11, 13
IL	133 (10)[e]	0.1-99,999	2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
IN	104 (7)[e]	0-999	2, 3, 5, 7, 8, 9, 10, 11, 12, 13
KS	26 (1)[e]	0-999	2, 3, 4, 5, 7, 8, 9, 11, 12, 13
KY	30 (2)[e]	0-9,999	1, 3, 8, 10, 11, 12, 13
LA	29 (1)[e]	0.1-49,999	1, 2, 3, 4, 7, 8, 9, 11, 12, 13
MA	60 (5)[e]	0-999	1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13
MD	21	0-99	3, 8, 9, 11, 12, 13
ME	5	0.1-99	11, 12, 13
MI	119 (8)[e]	0-999	2, 3, 7, 8, 9, 10, 11, 12, 13
MN	35 (2)[e]	0-9,999	2, 3, 4, 6, 8, 9, 10, 11, 12, 13

TABLE 4-2 (Continued)

State[b]	No. of facilities	Range of maximum amounts on site in thousands of pounds[c]	Activities and uses[d]
MO	72 (4)[e]	0-499,999	2, 3, 7, 8, 9, 10, 11, 12, 13
MS	21 (1)[e]	0-999	2, 8, 9, 11, 12, 13
MT	1	1-9	8, 11
NC	133 (13)[e]	0-999	3, 5, 7, 8, 9, 10, 11, 12, 13
ND	3	0.1-9	11, 12, 13
NE	14 (1)[e]	0.1-99	5, 7, 8, 9, 11, 12, 13
NH	23 (1)[e]	0-999	2, 3, 7, 8, 9, 10, 11, 12, 13
NJ	103 (7)[e]	0-49,999	1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13
NM	1	1-9	12, 13
NV	4 (1)[e]	0.1-99	9, 12
NY	85 (15)[e]	0.1-49,999	1, 2, 3, 7, 8, 9, 10, 11, 12, 13
OH	174 (10)[e]	0-49,999	2, 3, 7, 8, 9, 10, 11, 12, 13
OK	17	0.1-999	2, 4, 8, 9, 11, 12, 13
OR	13 (1)[e]	0.1-99	8, 9, 10, 11, 12, 13
PA	109 (5)[e]	0-499,999	1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13
PR	9 (2)[e]	0-999	8, 9, 12
RI	13 (1)[e]	1-99,999	3, 4, 8, 11, 12, 13
SC	36 (4)[e]	0.1-49,999	2, 3, 4, 7, 8, 9, 11, 12, 13
SD	5	1-99	8, 11, 13
TN	60 (6)[e]	0-9,999	2, 3, 5, 7, 8, 9, 11, 12, 13
TX	107 (2)[e]	0-49,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13

TABLE 4-2 (Continued)

State[b]	No. of facilities	Range of maximum amounts on site in thousands of pounds[c]	Activities and uses[d]
UT	10	0-99	8, 9, 11, 12, 13
VA	64 (1)[e]	0-49,999	3, 7, 8, 9, 10, 11, 12, 13
VT	4	1-9	8, 11, 12, 13
WA	32 (5)[e]	1-999	8, 10, 11, 12, 13
WI	71 (3)[e]	0-999	1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13
WV	8 (3)[e]	1-9,999	1, 3, 5, 6, 10, 11, 12, 13
WY	1	10-99	7

[a]TRI 1989
[b]Post office state abbreviations
[c]Data in TRI are maximum amounts on site at each facility.
[d]Activities/Uses:

1. produce
2. import
3. for on-site use/processing
4. for sale/distribution
5. as a byproduct
6. as an impurity
7. as a reactant
8. as a formulation component
9. as an article component
10. for repackaging only
11. as a chemical processing aid
12. as a manufacturing aid
13. ancillary or other use

[e]Number of facilities reporting "no data" regarding maximum amount of the substance on site.

4.4 DISPOSAL

Dilute solutions of 2-butanone can be discharged directly into sewage treatment facilities, sprayed into incinerators, or burned in paper packaging (OHM/TADS 1989). It can be destroyed in fluidized-bed incinerators, rotary kiln incinerators, or liquid injection incinerators using short residence times of a few seconds for either liquids or gases, and longer residence times for contaminated solids, if applicable (HSDB 1989). 2-Butanone has been reported to be amenable to biological degradation in sewage treatment plants (Babeu and Vaishnav 1987; Bridie et al. 1979; Gaudy et al. 1963.; Price et al. 1974; Urano and Kato 1986; Vaishnav et al. 1987; Young et al. 1968). No data are available regarding the amount disposed by each of these methods, nor is any information available regarding the trends in the disposal of 2-butanone.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

2-Butanone may be released to the atmosphere in fugitive emissions during its production, transport, and use. It is widely used in coating systems where its volatilization to the atmosphere is an intended outcome of its use. In urban areas, it can exist in the atmosphere as a result of automobile exhaust, the decomposition of other organic compounds, and from natural sources.

The release of 2-butanone to water or soil is not well documented. Release of 2-butanone to surface water may occur via industrial waste water emissions. 2-Butanone may also be released to soil or water from a spill or other catastrophic event. The leachate of landfills and hazardous waste sites may result in 2-butanone contamination of soil and groundwater.

According to the SARA Section 313 TRI (1989), an estimated total of 149,678,423 pounds of 2-butanone was released to the environment in 1987 by facilities that manufacture or process this compound. Of this, 149,478,640 pounds were released to the atmosphere. The quality of the TRI data must be viewed with caution since the 1987 data represent first-time, incomplete reporting of estimated releases by these facilities. Not all sources of chemical wastes are included and not all facilities. Only certain types of facilities were required to report. This is not an exhaustive list. These data are presented in Table 5-1.

2-Butanone is expected to rapidly volatilize from surface water and moist or dry soils to the atmosphere, In the atmosphere, this compound is expected *to* exist predominantly in the vapor phase. Wet deposition may return 2-butanone to the earth's surface.

In soil, 2-butanone is expected to display very high mobility, and it has the potential to leach into groundwater. This characteristic also suggests that it does not significantly adsorb to sediment and suspended organic matter in surface waters. 2-Butanone is not expected to bioconcentrate in fish and aquatic organisms.

Although the degradation of 2-butanone in the environment is understood on a theoretical level, data are not available to quantify all conclusions. In the atmosphere, 2-butanone is expected to undergo a vapor-phase reaction with photochemically produced hydroxyl radicals; the half-life for this process is approximately 1 day. However, laboratory experiments have suggested that the atmospheric half-life of 2-butanone is much shorter.

In water, 2-butanone is expected to undergo microbial degradation under both aerobic and anaerobic conditions. Chemical oxidation, direct photolysis, and hydrolysis of 2-butanone under environmental conditions are not expected to occur to any significant extent. Data on the fate of 2-butanone in soil are not available.

TABLE 5-1. Releases to the Environment from Facilities That Manufacture or Process 2-Butanone[a]

State[c]	No. of facilities	Range of reported amounts released in thousands of pounds[b]						
		Air	Underground injection	Water	Land	Total Environment[d]	POTW[e] transfer	Off-site waste transfer
AL	29	0-4,000	0-0	0-0	0-1	0-4,000	0-1	0-113
AR	41	0-968	0-0	0-0	0-17	0-968	0-50	0-70
AZ	21	0-125	0-0	0-0	0-0	0-125	0-0	0-151
CA	193	0-690	0-0	0-0	0-1	0-690	0-24	0-822
CO	14	0-159	0-0	0-0	0-0	0-159	0-0	0-8
CT	37	0-123	0-0	0-0	0-0	0-123	0-0	0-57
DE	10	0-623	0-0	0-0	0-0	0-623	0-10	0-230
FL	29	0-88	0-0	0-0	0-0	0-88	0-7	0-51
GA	58	0-812	0-0	0-0	0-0	0-812	0-12	0-692
IA	30	0-1,201	0-0	0-0	0-0	0-1,201	0-0	0-76
ID	1	2-2	0-0	0-0	0-0	2-2	0-0	14-14
IL	133	0-440	0-0	0-0	0-0	0-440	0-11	0-839
IN	104	0-1,400	0-0	0-0	0-0	0-1,400	0-1	0-466
KS	26	0-777	0-0	0-1	0-0	0-777	0-0	0-130
KY	30	0-130	0-0	0-0	0-0	0-130	0-0	0-390
LA	29	0-745	0-5	0-0	0-0	0-746	0-0	0-39
MA	60	0-601	0-0	0-0	0-0	0-601	0-27	0-508
MD	21	0-714	0-0	0-0	0-0	0-714	0-0	0-242
ME	5	0-111	0-0	0-0	0-0	0-111	0-0	0-30
MI	119	0-1,300	0-0	0-0	0-1	0-1,301	0-15	0-294
MN	35	0-10,219	0-0	0-0	0-4	0-10,219	0-0	0-1,734
MO	72	0-1,000	0-0	0-1	0-0	0-1,000	0-5	0-302
MS	21	1-4,529	0-0	0-0	0-0	1-4,529	0-4	0-1,290
MT	1	8-8	0-0	0-0	0-0	8-8	0-0	14-14
NC	133	0-980	0-0	0-0	0-0	0-980	0-0	0-276
ND	3	2-15	0-0	0-0	0-0	2-15	0-0	0-14
NE	14	0-277	0-0	0-0	0-0	0-277	0-0	0-8
NH	23	0-146	0-0	0-0	0-0	0-146	0-0	0-350
NJ	103	0-678	0-0	0-2	0-0	0-678	0-56	0-277
NM	1	12-12	0-0	0-0	0-0	12-12	0-0	0-0
NV	4	0-26	0-0	0-0	0-0	0-26	0-0	0-17
NY	85	0-470	0-0	0-3	0-0	0-470	0-59	0-196
OH	174	0-1,890	0-0	0-0	0-1	0-1,890	0-43	0-890
OK	17	0-1,242	0-0	0-0	0-0	0-1,242	0-0	0-555
OR	13	2-492	0-0	0-0	0-0	2-492	0-4	0-12
PA	109	0-1,259	0-0	0-2	0-4	0-1,259	0-4	0-264
PR	9	0-230	0-0	0-0	0-0	0-230	0-0	0-0
RI	13	0-542	0-0	0-0	0-0	0-542	0-0	0-110
SC	36	0-668	0-0	0-1	0-0	0-668	0-0	0-172
SD	5	19-48	0-0	0-0	0-0	19-48	0-0	0-40
TN	60	0-504	0-0	0-1	0-1	0-504	0-1	0-166
TX	107	0-1,304	0-52	0-9	0-1	0-1,304	0-6	0-400

TABLE 5-1 (Continued)

State[c]	No. of facilities	Range of reported amounts released in thousands of pounds[b]						
		Air	Underground injection	Water	Land	Total Environment[d]	POTW[e] transfer	Off-site waste transfer
UT	10	0-48	0-0	0-0	0-0	0-48	0-0	0-15
VA	64	0-1,495	0-0	0-0	0-10	0-1,495	0-3	0-214
VT	4	1-55	0-0	0-0	0-0	1-55	0-0	1-9
WA	32	0-2,130	0-0	0-0	0-1	0-2,130	0-1	0-180
WI	71	0-890	0-0	0-39	0-0	0-890	0-91	0-720
WV	8	0-235	0-0	0-6	0-0	0-235	0-2	0-45
WY	1	83-83	0-0	0-0	0-0	83-83	0-0	0-0

[a]TRI 1989
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviation
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility.
[e]publicly owned treatment works

5. POTENTIAL FOR HUMAN EXPOSURE

Various data are available regarding the concentration of 2-butanone in environmental media. It has been qualitatively detected in U.S. drinking water supplies and as a naturally occurring constituent of foods. It has also been detected in the air.

EPA has identified 1,177 NPL sites. 2-Butanone has been found at 137 out of the sites evaluated for its presence. However, we do not know how many of the 1,177 NPL sites have been evaluated for this chemical. As more sites are evaluated by EPA, this number may change (View 1989). The frequency of these sites within the United States can be seen in Figure 5-1.

The general population is exposed to 2-butanone by drinking contaminated water or by the ingestion of food containing it. Members of the general population living near hazardous waste sites may be exposed to contaminated drinking water if their household water source is well water. The general population is also expected to be exposed to 2-butanone by inhalation, especially in urban areas. The use of commercial coatings containing 2-butanone also results in exposure by inhalation, and possibly by dermal contact as well. High levels of exposure may occur for members of the general population if these coatings are used in an enclosed, unventilated area. Occupational exposure to 2-butanone may occur by inhalation during the production, formulation, use, or transport of this compound.

5.2 RELEASES TO THE ENVIRONMENT

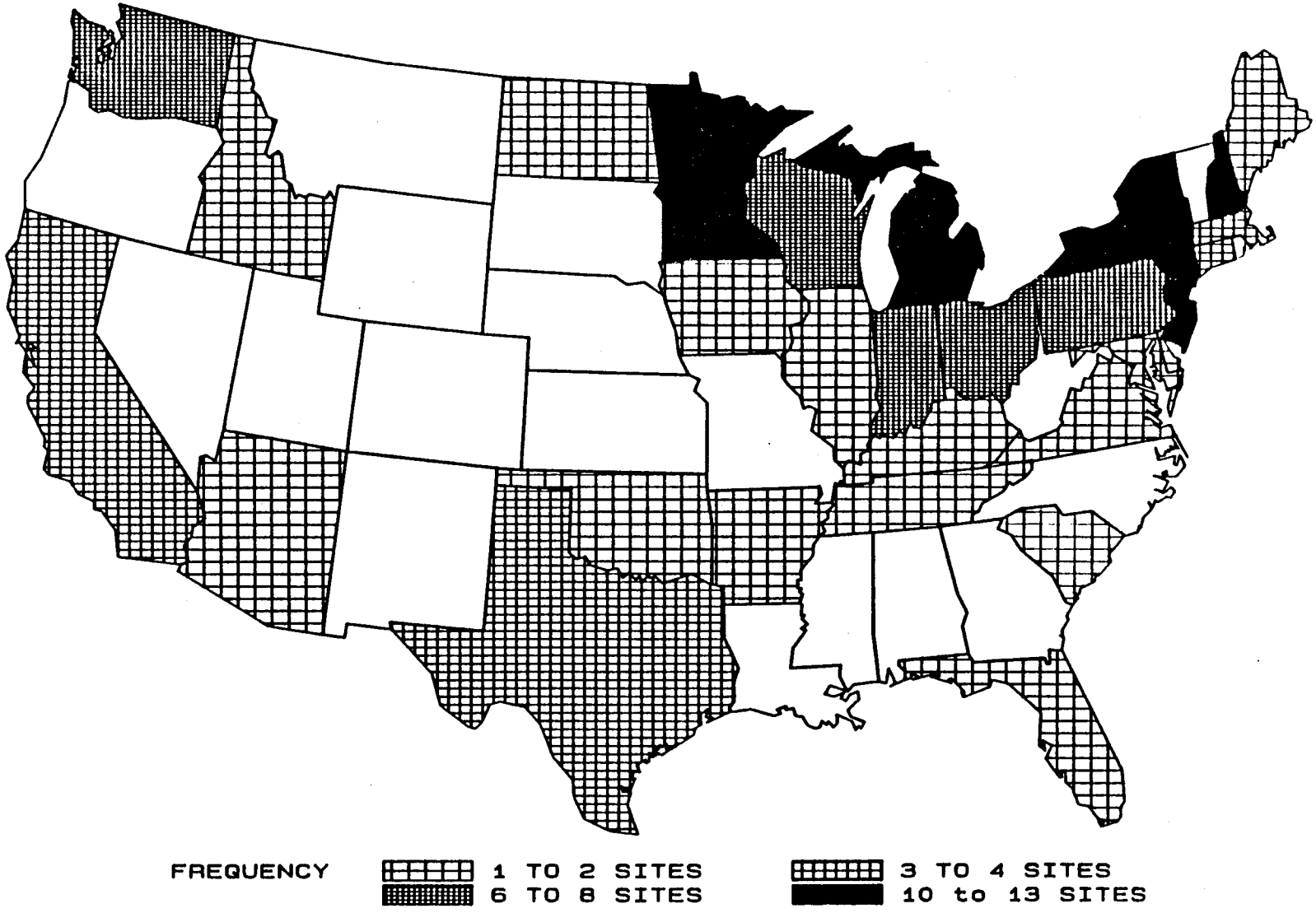
5.2.1 Air

2-Butanone may be emitted to the atmosphere during its production, formulation, storage, or use in commercial products. 2-Butanone may also be released to the atmosphere as a result of its use as a solvent in commercial products. It was identified as an emission from a variety of indoor building materials: latex caulk, particle board, latex paint, and polyurethane floor finish (Tichenor 1987; Tichenor and Mason 1988). Since 2-butanone is prevalent in adhesives and coatings (Papa and Sherman 1981), it may be released to the atmosphere during the curing of these products.

According to the SARA Section 313 TRI (1989), an estimated total of 149,478,640 pounds of 2-butanone was released to the atmosphere in 1987 by facilities that manufacture or process this compound. The quality of the TRI data must be viewed with caution since the 1987 data represent first-time, incomplete reporting of estimated releases by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list.

2-Butanone is present in the exhaust of automobiles (Seizinger and Dimitriades 1972). In a Swedish study, 2-butanone was detected in automobile exhaust, although the ambient air levels measured in Stockholm did not correlate with these emissions (Jonsson et al. 1985). Thus, the prevalence of other sources is indicated, as the air levels of 2-butanone were higher than

FIGURE 5-1. FREQUENCY OF NPL SITES WITH 2-BUTANONE CONTAMINATION *



* Derived from View 1989

could be explained solely by automobile emissions. Other potential sources of 2-butanone in the atmosphere include the burning of polyethylene (Hodgkin et al. 1982) and the photochemical degradation of hydrocarbons (Grosjean 1982), especially those emitted from motor vehicles. 2-Butanone is also emitted to the atmosphere from such natural sources as European firs, junipers, cedars, cypress trees, and ferns (Isidorov et al. 1985) and ant secretions (Cammaerts et al. 1978).

5.2.2 Water

Limited data are available regarding the release of 2-butanone to surface and groundwaters. It has been detected in waste water effluents from commercial processes (Dunovant et al. 1986; Hawthorne and Sievers 1984; Jungclaus et al. 1978; Pellizzari et al. 1979). 2-Butanone may also be present in water from the microbial oxidation of butane (Phillips and Perry 1974). Its relatively high water solubility, 136,000 mg/L at 25°C (Tewari et al. 1982), suggests that wet deposition of atmospheric 2-butanone results in the contamination of surface water. Evidence for this comes from the fact that 2-butanone has been detected in rain water (Grosjean and Wright 1983).

According to the SARA Section 313 TRI (1989), an estimated total of 75,858 pounds of 2-butanone was released to water in 1987 by facilities that manufacture or process this compound, a very small amount compared to what is released to the atmosphere. The quality of the TRI data must be viewed with caution since the 1987 data represent first-time, incomplete reporting of estimated releases by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list.

The contamination of groundwater with 2-butanone has occurred at hazardous waste sites (Francis et al. 1980; Sawhney and Kozloski 1984) and landfills (Sabel and Clark 1984) due to infiltration of contaminated leachate. 2-Butanone was detected in 180 groundwater samples from 357 hazardous waste sites monitored by the Contract Laboratory Program (CLP) at a geometric mean concentration of 302 ppb for the positive samples (CLPSD 1988). Note that the CLPSD includes data from both NPL and non-NPL sites. 2-Butanone is also likely to enter groundwater as a result of a spill to soil during a catastrophic event, such as a tanker spill (Halvorsen and Ohneck 1985).

2-Butanone may also enter water from natural sources. It has been detected in various species of macroalgae at concentrations as high as 2,600 ng/g (Whelan et al. 1982).

5.2.3 Soil

Limited data are available regarding the release of 2-butanone to soil. The presence of this compound in the groundwater at hazardous waste sites and landfills (Francis et al. 1980; Sabel and Clark 1984; Sawhney and Kozloski 1984) suggests that leachate at these facilities will be a source of

2-butanone release to soil. Wet deposition of atmospheric 2-butanone may also result in its contamination of soil. 2-Butanone may enter soil during a catastrophic event, such as a tanker spill (Halvorsen and Ohneck 1985). 2-Butanone has been found in 309 of 357 hazardous waste sites monitored by the CLP at a geometric mean concentration of 87 ppb (CLPSD 1988). Note that the CLPSD includes data from both NPL and non-NPL sites.

According to the SARA Section 313 TRI (1989), an estimated total of 48,675 pounds of 2-butanone was released to soil in 1987 by facilities that manufacture or process this compound; a very small amount compared to what is released to the atmosphere. The quality of the TRI data must be viewed with caution since the 1987 data represent first-time, incomplete reporting of estimated releases by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

In the atmosphere, 2-butanone is expected to exist predominantly in the vapor phase (Eisenreich et al. 1981; Riddick et al. 1986). This is consistent with experimental data, which demonstrated that the gas-phase concentration of 2-butanone in Los Angeles, California, was from 220 to 3,000 times greater than the particulate phase concentration (Grosjean 1982). The relatively high water solubility of 2-butanone, 136,000 mg/L at 25°C (Tewari et al. 1982), suggests that wet deposition may remove 2-butanone from the atmosphere. 2-Butanone has been identified in rain water (Grosjean and Wright 1983). The absence of significant amounts of particulate 2-butanone indicates that dry deposition to the earth's surface is not an important fate process. The short residence time expected for 2-butanone in the atmosphere, less than 1 day,suggests that it is not transported long distances from its original point of release.

Based on an experimental soil adsorption coefficient (K_{oc}) of 3.55 (Roy and Griffin 1985) 2-butanone is expected to display very high mobility in soil (Swann et al. 1983). 2-Butanone was found in groundwater samples shortly after a tanker spill (Halvorsen and Ohneck 1985) and in the groundwater underneath hazardous waste sites and public landfills (Francis et al. 1980; Sabel and Clark 1984; Sawhney and Kozloski 1984). The vapor pressure of 2-butanone, 90.6 mmHg at 25°C (Riddick et al. 1986), and the Henry's law constant, 5.77×10^{-5} atm m^3/mol at 25°C, suggest that volatilization from either dry or moist soil to the atmosphere will be an important environmental process.

If 2-butanone is released to water it is expected to rapidly volatilize to the atmosphere. Based on its Henry's law constant, an estimated volatilization half-life from a model river 1 m deep, flowing at 1 m/set with a wind velocity of 3 m/sec, is approximately 15 hours (Lyman et al. 1982).

2-Butanone is not expected to significantly adsorb to sediment and suspended organic matter. It is also not expected to bioconcentrate in fish and aquatic organisms (Lyman et al. 1982). These conclusions are based on an experimental K_{oc} of 3.55 (Roy and Griffin 1985), and a calculated bioconcentration factor of 0.98 obtained from its octanol/water partition coefficient, 0.29 (Hansh and Leo 1985), and an appropriate regression equation (Lyman et al. 1982).

5.3.2 Transformation and Degradation

5.3.2.1 Air

2-Butanone is expected to undergo atmospheric destruction by the gasphase reaction with photochemically produced hydroxyl radicals. Rate constants for this reaction ranging from 1.85×10^{-11} to 9.8×10^{-13} atm/molecule-sec in the temperature range of 22-32°C have appeared in the literature (Cox et al. 1980, 1981; Edney and Corse 1986; Edney et al. 1986; Darnall et al. 1976; Gusten et al. 1984; Wallington and Kurylo 1987; Wallington et al. 1988). Using a recommended rate constant of 1.85×10^{-11} atm/molecule-sec at 25°C and an average atmospheric hydroxyl radical concentration of 5×10^5 molecule/cm^3 (Atkinson 1985), a half-life of 21 hours for this reaction can be calculated. However, experiments performed under simulated atmospheric conditions in the laboratory have shown that 2-butanone has a half-life of only 9.8 hours for photo-initiated processes (Dilling et al. 1976). The rate of its destruction increased in the presence of other anthropogenic compounds. The atmospheric destruction of 2-butanone as a result of direct irradiation is not expected to be significant under atmospheric conditions (Cox et al. 1980). Therefore, direct photolysis cannot account for the enhanced rate of atmospheric destruction observed in the laboratory. However, the data suggest that other mechanisms are responsible for the destruction of 2-butanone in the atmosphere, which are yet to be defined.

5.3.2.2 Water

2-Butanone is expected to be removed from environmental waters by microbial degradation under both aerobic and anaerobic conditions. Limited data specific to the chemical degradation of 2-butanone in water are available; however, it is not expected to occur to any significant extent.

Numerous investigations have concluded that 2-butanone undergoes biological degradation under aerobic conditions. At an initial concentration of 1 ppm, 2-butanone completely degraded in aerated water obtained from a deep Florida aquifer within 14 days after a 5-day lag period (Delfino and Miles 1985). Screening studies using a microbial seed from domestic waste treatment plants have indicated that 2-butanone has a 5-day biological oxygen demand (BOD_5) which is between 59% and 74% of the theoretical amount after a short lag period (Babeu and Vaishnav 1987; Bridie et al. 1979; Gaudy et al. 1963; Price et al. 1974; Urano and Kato 1986; Vaishnav et al. 1987; Young et al.

1968). A pure culture study indicated that propionate is produced as a result of the microbial oxidation of 2-butanone (Phillips and Perry 1974).

2-Butanone has been listed as a compound amenable to degradation by anaerobic biotechnology (Speece 1983). At an initial concentration of 500 ppm, 2-butanone was completely reduced to methane within 8 days in a fermentor using a domestic sludge inoculum that had been adapted to acetate (Chou et al. 1979).

An experimentally determined rate constant of 5.4×10^{8} L/mol-sec has been determined for the reaction of 2-butanone with hydroxyl radicals in water (Anbar and Neta 1967). This value corresponds to a half-life of 4 years for this reaction, given a hydroxy radical concentration of 1×10^{-17} M (Mill et al. 1980). Hydrolysis of ketones is generally not believed to be an environmentally important process (Lyman et al. 1982; Mill 1982). A rate constant of 0 L/mol-year was listed for the hydrolysis of 2-butanone under neutral, acidic, and basic conditions at 25°C (Kollig et al. 1987), indicating that this process does not occur in the environment. By analogy to the gasphase photolysis of 2-butanone (Cox et al. 1980), direct photochemical breakdown of 2-butanone in water is not expected. Therefore, the chemical degradation of 2-butanone in environmental waters is not expected to occur to any significant extent.

The chemical alteration of 2-butanone in rain water has been postulated. In acid rain, hydroxy sulfonates may be formed by the reaction with bisulfite, and ammonia adducts may be formed in ammoniated rain (Grosjean and Wright 1983). The concentration of these reactive species is likely to be much higher in rain water than in surface water; therefore, a more rapid rate of reaction would be expected in rain.

5.3.2.3 Soil

No specific data concerning the fate of 2-butanone in soil were available. By analogy to the experimental results on the microbial degradation of 2-butanone in water, this compound may degrade in soil under aerobic and anaerobic conditions given suitable time for adaptation of the microbial population. Again by using an analogy to the fate of 2-butanone in aqueous systems, it is not expected to hydrolyze, photolyze on the surface, or undergo chemical degradation.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

2-Butanone has been detected in a limited number of sites in rural, urban, and indoor locations. It was detected in 17 samples taken in Tucson, Arizona, in 1982 at an average concentration of 2.8 ppb. In the mountains of Arizona, the concentration was 0.50 ppb (Snider and Dawson 1985). The range

of 2-butanone measured in Los Angeles air in 1980 was.O-14 ppb in 70 samples (Grosjean 1982). 2-Butanone was found in one-third of samples taken downwind of a solvent recycling facility in Maryland in 1970, at a maximum concentration of 94 ppm (Smoyer et al. 1971). Although it has been detected in the exhaust of gasoline engines, it was not found in the air of a highway mountain tunnel (Hampton et al. 1982).

2-Butanone was detected in the air of the Kin-But chemical waste site, located in New Jersey, at concentrations ranging from trace to 1.5 pg/m3 (0.51 ppb), and 0.5 to 33 μg/m^3 (0.17-11.3 ppb) in samples surrounding the site (Pellizzari 1982). It was qualitatively detected in the air at four of four hazardous waste sites and one landfill in New Jersey (LaRegina et al. 1986).

In a survey of 36 homes taken in Chicago, Illinois, 2-butanone was detected in the indoor air at 3 residences (Jarke et al. 1981). It was also found in three outdoor samples in this survey. It is not clear, however, if the positive indoor and outdoor samples were collected at the same location. In a compilation and analysis of ambient monitoring data collected from 1970 to 1987, the daily concentration of 2-butanone was 0 ppb in urban, suburban, and rural areas (Shah and Heyerdahl 1988). 2-Butanone has been qualitatively detected in the indoor air of homes in Chicago (Jarke et al. 1981) and in Canadian residential and office buildings (Tsuchiya 1987).

The sporadic ambient air monitoring data available for 2-butanone suggest that the average background concentration of this compound may be very low. However, the available data also suggest that there are dramatic, temporal, and diurnal variations in its concentration.

5.4.2 Water

Numerous studies have qualitatively detected 2-butanone in drinking water supplies (Kool et al. 1982). It has been found in drinking water from the District of Columbia; Cincinnati, Ohio; Miami, Florida; Ottumwa, Iowa; Philadelphia, Pennsylvania; Seattle, Washington; Tuscaloosa, Alabama; and New Orleans, Louisiana (Bertsch et al. 1975; Coleman et al. 1976; EPA 1974, 1975; Kopfler et al. 1977; Scheiman et al. 1974). It was detected in Des Moines, Iowa, drinking water samples at an estimated concentration of 1.6 ppb (Ogawa and Fritz 1985). 2-Butanone was detected in tap water 8 months after the installation of new polyvinyl chloride (PVC) pipes at a concentration ranging from 0.4 to 4.5 ppm (Wang and Bricker 1979). It resulted from the glue used to cement the water pipes together. The concentration of 2-butanone in the water increased with the amount of time the water sat in the pipes.

2-Butanone has been qualitatively detected in rain water and the clouds of Henninger, California, at 0.04 ppb, and in the mist of Long Beach, California (Grosjean and Wright 1983). Trace amounts have also been found in the ice in Fairbanks, Alaska (Grosjean and Wright 1983).

5. POTENTIAL FOR HUMAN EXPOSURE

2-Butanone was listed as being detected in less than 5% of U.S. groundwater supplies (Dyksen and Hess 1982). At U.S. hazardous waste sites, 2-Butanone was listed as being frequently detected in the groundwater (Garman et al. 1987). This statement should be interpreted with caution, as "frequently" was defined as greater than 0.1%, of the samples. 2-Butanone was detected in 180 groundwater samples from 357 hazardous waste sites monitored by the CLP at a geometric mean concentration of 302 ppb in the positive samples (CLPSD 1988). Examples of.the presence of 2-butanone at hazardous waste sites and landfills can be found in Table 5-2. It was detected in groundwater samples underneath a tanker truck spill at concentrations up to 2,200 ppm (Halvorsen and Ohneck 1985). Interpretation of the concentration of 2-butanone found in groundwater samples should be made carefully, and should take into account the experimental methods used in the determinations; results may be skewed due to the presence of 2-butanone in the adhesives used to cement PVC well pipes together (Sosebee et al. 1983).

2-Butanone has been detected in the effluent of various industrial processes. It was found in six of seven waste water samples from energyrelated processes at a concentration up to 645 ppb (Pellizzari et al. 1979). 2-Butanone was detected in the waste water of a specialty chemical manufacturing plant at a concentration of 8-20 ppm, but not in the receiving river water or its sediment (Jungclaus et al. 1978). It was also detected in the waste water from shale oil processing at a concentration of 0.4-18 ppm (Hawthorne and Sievers 1984).In 1982, 2-butanone was detected at concentrations of 83 ppb or less in the waste water entering Cincinnati treatment plants (Dunovant et al. 1986).

2-Butanone has been detected in 77 of 357 surface water samples at U.S. hazardous waste sites at a geometric mean concentration of 11 ppb for the positive samples (CLPSD 1988). It was qualitatively detected in the Black Warrier River, located in Tuscaloosa, Alabama (Bertsch et al. 1975), and in sea water from the straits of Florida at O-22 ppb in 1968 (Corwin 1969).

5.4.3 Soil

Limited data are available on the detection of 2-butanone in soil samples. It has been found in 309 of 357 hazardous waste sites monitored by the CLP at a geometric mean concentration of 87 ppb for the positive samples (CLPSD 1988).

5.4.4 Other Environmental Media

2-Butanone has been detected as a natural component of numerous types of foods. It has been qualitatively identified as a volatile constituent in raw chicken breast muscle, milk, roasted filberts (nuts), Beaufort (Gruyere) and cheddar cheese, bread dough, and intact tree-ripened nectarines (Dumont and Adda 1978; Gordon and Morgan 1979; Grey and Shrimpton 1967; Keen et al. 1974;

TABLE 5-2. Detection of 2-Butanone in the Groundwater of Hazardous Waste Sites and Landfills

Type/Location	Sampling Dates	No. of Samples	No. of Positive	Concentration	Reference
Waste sites, groundwater					
Connecticut	1982-1983	5	1	4,800 ppm	Sawhney and Kozloski 1984
Low-level radioactive					
Waste sites, surface water					
Valley of the Drums, KY	No data	No data	No data	≤690 ppb	Stonebraker and Smith 1980
Landfills, groundwater					
Municipal solid waste	No data	13	7	6.8-6,200 ppb	Sabel and Clark 1984
Landfills, leachate					
Municipal solid waste	No data	6	6	110-27,000 ppb	Sabel and Clark 1984

Kinlin et al. 1972; Sosulski and Mahmoud, 1979; Takeoka 'et al. 1988). The mean concentration of 2-butanone in dried beans, split peas, and lentils was 148, 110, and 50 ppm, respectively (Lovegren et al. 1979). 2-Butanone has been detected in southern peas at a median concentration of 120 ppb (Fisher et al. 1979), and it has been qualitatively detected in winged beans and soybeans (Del Rosario et al. 1984). It has also been detected in cigarette smoke (Higgins et al. 1983; Osborne et al. 1956).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Available monitoring data suggest that the general population is exposed to 2-butanone. In the early stages of the Total Exposure Assessment Methodology (TEAM) study, 2-butanone was qualitatively detected in 3 of 8 personal air samples, 5 of 12 breath samples, and 1 of 1 drinking water sample obtained from 12 volunteers living in urban areas of New Jersey or North Carolina (Wallace et al. 1984). 2-Butanone has also been detected in the expired air of 206 of 387 samples (53.2%) taken from 54 adult, nonsmoking, urban dwelling subjects, at an average concentration of 3.6 ng/L (Krotoszynski et al. 1979). It was detected in the expired air of six of eight male volunteers, three of whom were smokers (Conkle et al. 1975). 2-Butanone was found in 5 of 12 samples of human mothers' milk from subjects in 4 different U.S. urban areas (Pellizzari et al. 1982). It has been qualitatively detected in the indoor air of homes in Chicago (Jarke et al. 1981) and in Canadian residential and office buildings (Tsuchiya 1987).

Exposure to 2-butanone by the general population may occur by ingestion of contaminated drinking water. This compound has been identified in U.S. drinking water supplies (Bertsch et al. 1975; Coleman et al. 1976; EPA 1974, 1975; Kopfler et al. 1977; Ogawa and Fritz 1985; Scheiman et al. 1974). Inhalation is also a likely route of exposure to 2-butanone, especially during the household use of commercial coatings that use 2-butanone as a solvent. Exposure by dermal contact may also occur during the use of such coatings.

2-Butanone is a naturally occurring constituent in a variety of common foods (Del Rosario et al. 1984; Dumont and Adda 1978; Gordon and Morgan 1979; Grey and Shrimpton 1967; Keen et al. 1974; Kinlin et al. 1972; Lovegren et al. 1979; Takeoka et al. 1988). Ingestion of these foods will result in exposure to 2-butanone. Exposure to 2-butanone may also occur while smoking (Higgins et al. 1983; Osborne et al. 1956). Students taking undergraduate general chemistry laboratory courses may be also exposed to 2-butanone (Kolb 1988).

According to the National Occupational Exposure Survey (NOES) conducted by NIOSH between 1980 and 1983, 1,221,587 workers, of which 201,308 were women, were potentially exposed to 2-butanone during that time period (NIOSH 1989). Of these workers, 84% (80% for the women) were exposed during the use of trade name products containing 2-butanone. Occupational exposure is expected to occur by inhalation and dermal contact.

A study of three companies involved in spray painting and spray gluing operations reported that, for 89 workers exposed to 2-butanone, the mean air concentration was 0.3 ppm (Whitehead et al. 1984). 2-Butanone was detected in the air of Cincinnati waste water treatment plants in 1982; 3 of 17 samples were positive at concentrations of 5.7 ppb or less (Dunovant et al. 1986). It has also been detected in the air above shale oil waste waters (Hawthorne and Sievers 1984). The breathing zone air for workers at an organic solvent recycling plant averaged 11 ppm during drum decantation operations, and 10 ppm during all other work activities (Kupferschmid and Perkins 1986). The ambient concentration was not greater than exposure limits of 200 ppm in any of these examples (NIOSH 1984). The concentrations of 2-butanone in air samples obtained from the Skylab, 1973-74, ranged from 2.4 to 1,505 ppb (Liebich et al. 1975). Personal exposure to 2-butanone at a waste solvent incineration facility ranged from <O.Ol to 1.2 ppm (Decker et al. 1983).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

For the general population, high levels of exposure to 2-butanone may occur for those living near commercial settings where this compound is used. For example, the downwind 2-butanone concentration near a solvent recycling facility was measured at concentrations up to 94 ppm (Smoyer et al. 1971). High levels of exposure may also occur during the use of commercial coatings containing 2-butanone, especially when working in enclosed, unventilated spaces. Members of the general population living near hazardous waste sites and drawing their drinking water from groundwater sources may be exposed to high levels of 2-butanone through ingestion of contaminated water, although no information on the size of the population can be provided.

High levels of occupational exposure to 2-butanone may occur by inhalation and dermal contact during the loading and unloading of large quantities of this material during shipment. The application of commercial coatings containing 2-butanone without adequate protection may also lead to high levels of exposure, primarily by inhalation.

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-butanone is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 2-butanone.

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. The physical and chemical properties of 2-butanone are well documented. The environmental fate of 2-butanone can be predicted from these properties and compared to experimental results once they are obtained in areas where deficiencies exist.

Production, Import/Export, Use, and Disposal. The significant amounts of 2-butanone produced in the United States, combined with its prevalence in commercial and household products, suggest that large numbers of citizens are potentially exposed to,anthropogenic sources of this $ompound. The production, use, and international trading of 2-butanone is well described in the available literature (Chemical Marketing Reporter 1987; Neir and Strehlke 1985; Papa and Sherman 1981; USITC 1987, 1988, 1989). Methods for the disposal of 2-butanone are established (HSDB 1989; OHM/TADS 1989), but the amounts processed by each method cannot be ascertained. Therefore, disposal of 2-butanone cannot be compared to the regulations controlling this practice. Knowing the amount of 2-butanone released to the environment and its disposal pattern will aid in determining routes and levels of exposure to the general population by indicating which media should be monitored carefully.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to EPA. The Toxic Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. There is sufficient predictive information to indicate that 2-butanone is not likely to partition from water (Hansch and Leo 1985; Lyman et al. 1982; Roy and Griffen 1985); yet, there are few field studies to verify these predictions. Similarly, 2-butanone's transport, transformation, and degradation in the environment can be predicted (Atkinson 1985; Babeu and Vaishnav 1987; Cox et al. 1980; Delfino and Miles 1985), but not as yet experimentally substantiated in all areas. Experimental studies in this area would allow the determination of 2-butanone's lifetime in the environment and aid in determining levels and routes of human exposure.

Bioavailability from Environmental Media. Numerous toxicokinetic and toxicity studies in humans and animals have demonstrated the bioavailability of 2-butanone from air, ingestion of food and water, and dermal contact. Absorption of 2-butanone after inhalation is well established, and it appears to be adsorbed after ingestion. These mechanisms are consistent with what one would expect, based on 2-butanone's physical and chemical properties (Lyma

et al. 1982). Given the potential for exposure to 2-butanone because of its prevalence in commercial products available to the public (Neier and Strehlke 1985) and its ability to enter the immediate areas of the environment (TRI 1989), further research on the bioavailability of this compound will allow the quantification of human exposure and risk.

Food Chain Bioaccumulation. 2-Butanone is not believed to appreciably bioconcentrate in fish and aquatic organisms (Hansch and Leo 1985; Lyman et al. 1982). It is also not expected to biomagnify in the food chain. Quantitative data supporting these conclusions are not available in the literature. Additional information on bioconcentration and biomagnification would be useful in confirming the predicted behavior of this compound.

Exposure Levels in Environmental Media. Data are available regarding the level of 2-butanone in endronmental media (Grosjean and Wright 1983; Shah and Heyerdahl 1988) and foods (Dumont and Adda 1978; Grey and Shrimpton 1967; Kinlin et al. 1972; Lovegren et al. 1979; Takeoka et al. 1988); however, the data available are often qualitative and only generalized trends regarding the occurrence of this compound can be derived. Its presence in environmental media near hazardous waste sites is not well documented (CLPSD 1988). Quantitative determination of the levels of 2-butanone in environmental media and foods will allow the estimation of levels on human intake of this compound from each media.

Exposure Levels in Humans. 2-Butanone has been found in the human blood samples of urban dwellers, but the observed levels have not been correlated with personal activities. Studies on the level of 2-butanone in human tissues near hazardous waste sites are not complete. A correlation of the levels of 2-butanone in humans with their personal activities or the areas where they live will allow an assessment of potential exposure to the general population. Similarly, correlations of occupational exposure by profession will allow a determination of human exposure levels.

Exposure Registries. No exposure registries for 2-butanone 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 the compound.

5.7.2 On-going Studies

On-going studies on water purification techniques and transformation of 2-butanone in the environment have been identified (EPA 1989b), although no specific information was provided.

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, will be analyzing human blood samples for 2-butanone and other volatile organic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

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-butanone 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-butanone. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect 2-butanone in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Numerous procedures that detect-2-butanone in biological materials have been reported in the literature. A summary of.these methods is found in Table 6-l. In general, each technique appears to be capable of determining 2-butanone in any type of biological matrix given suitable modification of the sample collection/preparation step.

Since 2-butanone is a volatile compound, analysis by headspace sampling can be accomplished for both liquid matrices, such as blood and urine (Deveaus and Huvenne 1987; Perbellini et al. 1984), and solid matrices, such as soft tissue (Perbellini et al. 1984). For solid samples such as soft tissue, better results are obtained if the sample is first homogenized at low temperatures before analysis. The technique involves gently heating the sample in a closed system, followed by withdrawing a portion of the air above the sample (the headspace) by syringe. Separation of 2-butanone from other compounds that may be present is then accomplished by injecting the contents of the syringe directly into a gas chromatograph (GC). As indicated in Table 6-2, successful quantification of 2-butanone has been accomplished using a variety of detection systems, including a flame ionization detector, mass spectrometer, or Fourier transform infrared spectrometer.

Analysis of 2-butanone in liquid samples can also be accomplished by purge and trap methodology (Pellizzari et al. 1982). In this technique, an inert gas is bubbled through the sample, liberating 2-butanone. The contaminant is then trapped on an adsorbent cartridge, followed by thermal desorption directly into a gas chromatograph (GC). This technique has been successfully used for analysis of human milk samples (Pellizzari et al. 1982)

Extractive techniques can also be used for the analysis of 2-butanone in liquid samples (Kezic and Monster 1988; Van Doorn et al. 1989). The sample is shaken with an immiscible organic solvent into which 2-butanone partitions.

TABLE 6-1. Analytical Methods for Determining 2-Butanone in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit (ppm)	Percent recovery	Reference
Urine	Derivatization with o-nitrophenol-hydrazine, liquid-liquid extraction by HPLC	HPLC/UV	0.10	No data	Van Doorn et al. 1989
Urine	Acidification, extraction with CH_2Cl_2 by HPLC, concentration	GC/FID	0.01	85%-91%	Kezic and Monster 1988
Urine	Headspace analysis	GC/MS	No data	No data	Perbellini et al. 1984
Blood	Heat sample to 80°C in sealed tube, obtain headspace sample	GC/FTIR	6	No data	Deveaux and Huvenne 1987
Blood	Derivatization with o-nitrophenyl-hydrazine, liquid-liquid extraction by HPLC	HPLC/UV	0.10	No data	Van Doorn et al. 1989
Blood	Headspace analysis	GC/MS	No data	No data	Perbellini et al. 1984
Milk	Purge at elevated temperatures, trap on Tenax cartridges, thermal desorption	GC/MS	No data	No data	Pellizzari et al. 1982
Soft tissue	Homogenize sample at 4°C, heat to 80°C in sealed tube, obtain headspace sample	GC/FTIR	6	No data	Deveaux and Huvenne 1987
Soft tissue	Headspace analysis	GC/MS	No data	No data	Perbellini et al. 1984
Expired air	Collect breath in Tedlar bag pump air through Tenax cartridges, thermal desorption	GC/MS	No data	No data	Wallace et al. 1984

FID = flame ionization detector
FTIR = Fourier transform infrared spectrometry
GC = gas chromatography
HPLC = high performance liquid chromatography
MS = mass spectrometry
UV = ultraviolet spectroscopy

TABLE 6-2. Analytical Methods for Determining 2-Butanone in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Pump air through sorbent tube, desorb with CS_2 - NIOSH 2500	GC/FID	4 μg	92%	NIOSH 1984
Air	Pump air through cryogenic trap, attach trap to GC, thermal desorption	GC/FID	8 ppb	No data	Jonsson et al. 1985
Water	Purge and trap	GC/FID GC/MS	10 ppb	No data	EPA 1988
Drinking water	Purge and trap on a Tenax cartridge	GC/FID	No data	No data	Wallace et al. 1984
Soil	Add water, heat to 40°, purge and trap, thermal desorbtion	GC/FID GC/MS	10 ppb	No data	EPA 1988
Sediment	Add water, heat to 40°, purge and trap, thermal desorbtion	GC/FID GC/MS	10 ppb	No data	EPA 1988

FID = flame ionization detector
GC = gas chromatography
MS = mass spectrometry

After concentrating the extract, the sample can be analyzed by different methods. 2-Butanone can first be derivitized to increase its extraction efficiency, or to make it more visible to the detection system.

Numerous types of detection and quantitation methods have been used in the analysis of 2-butanone in biological samples. Gas chromatography has been used to separate 2-butanone from other contaminants that may be present. Direct quantitation can be made by using a flame ionization detector (FID), tandem gas chromatography-mass spectrometry (GC-MS), or tandem GC-fourier transform infrared spectrometry (GC-FTIR). The latter two techniques also allow direct identification of the contaminants. Analysis of derivitized 2-butanone can be accomplished using high-performance liquid chromatography (HPLC) equipped with an ultraviolet (WV) detector. These detection systems are capable of measuring 2-butanone in the sub-ppm range; the limits on the GC-FTIR system are slightly greater than 1 ppm.

Given the numerous techniques available for the determination of 2-butanone in biological samples, and the lack of any standardized method for each individual matrix, the choice of an analysis technique appears to be a function of the instrumentation and personal biases of the laboratory performing the analysis. With the exception of the derivitization method, all of the techniques described above are also capable of determining the metabolites of 2-butanone (3-hydroxy-2-butanone, 2-butanol, and 2,3-dihydroxybutane) in biological samples.

6.2 ENVIRONMENTAL SAMPLES

A short description of standardized methods that can be used for the analysis of 2-butanone in environmental samples is presented in Table 6-2. It should be noted that an extensive list of methods for the analysis of 2-butanone in environmental samples can be compiled from the literature. In all of these methods, however, there is a consensus that, after the sample preparation stage, mixture separation and quantitative analysis are best determined by the use of a gas chromatograph coupled with any of an assortment of detectors (Bertsch et al. 1975; Coleman et al. 1976; Corwin 1969; Dunovant et al. 1986; Hawthorne and Sievers 1984; Isidorov et al. 1985; Jonsson et al. 1985; Jungclaus et al. 1978; LaRegina et al. 1986; Pellizzari 1982; Sawhney and Kozloski 1984; Smoyer et al. 1971; Snider and Dawson 1985; Wallace et al. 1984; Wang and Bricker 1979).

The analysis of 2 butanone in air can be accomplished by NIOSH method 2500 (NIOSH 1984). The sample is obtained in the field by the use of a pumping system to pass a measurable quantity of air (approximately l-12 L) through a tube loaded with a solid sorbent, Ambersorb XE-347. Extraction of the tube with the solvent carbon disulfide liberates the 2-butanone, and quantitation is achieved by GC using a flame ionization detector.

6. ANALYTICAL METHODS

The analysis of 2-butanone in soil, sediment, and water samples at hazardous waste sites is described in the Contract Laboratory Program manual (EPA 1988). For the soil and sediment samples, the procedure begins with the addition of a small portion of water to the sample. At this point, all three matrices are subjected to a purge and trap cycle. An inert gas is bubbled through the sample, volatilizing 2-butanone. The gas stream is then passed through an adsorbent tube that recollects the 2-butanone. The sorbent tube is attached to a gas chromatograph and heated to flush the sample onto a GC column. Quantification can be accomplished using either a flame ionization detector or a mass spectrometer, depending on the total concentration of organics in the sample. Required quantitation limits for this program are 10 ppm in all three matrices. No other standardized methods for the determination of 2-butanone in environmental samples were located.

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-butanone is available. Uhere adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 2-butanone.

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. Numerous methods for the determination of 2-butanone in biological materials have been described in the literature (Deveaux and Huvenne 1987; Kezic and Monster 1988; Pellizzari et al. 1982; Perbellini et al. 1984; Van Doorn et al. 1989). These methods are also appropriate for determining the metabolites of 2-butanone, 3-hydroxy-2-butanone, 2-butanol, and 2,3-dihydroxybutane, which also serve as biomarkers of exposure. These methods display the requisite sensitivity to measure background levels in the population and levels which may indicate a concern for biological effects. Standardized methods for these procedures should be established as no standardized methods could be located. Any methodology established for determining biomarkers of exposure must take into account the short biological half-life of 2-butanone, which may render these methods inferior to direct measurements of exposure.

There are no known biomarkers of effect which are specific to 2-butanone.

Methods for Determining Parent Compounds and Degradation Products in Snvironmental Media. Numerous methods capable of detecting low levels of 2-butanone in environmental media have been described in the literature (Bertsch et al. 1975; Dunovant 1985; Hawthorne and Sievers 1984; LaRegina et al. 1986; Pellizzari 1982; Wallace et al. 1984). Appropriate standardized methods are available for the determination of 2-butanone in air (NIOSH 1984), water, soil, and sediments (EPA 1988) at levels that may constitute a concern for human health. The methods for determining 2-butanone in air, the medium that represents the most concern for exposure, are highly sensitive, accurate, and reproducible. The exact levels of detection for these methods in all media, however, are not described. There are numerous reliable methods available in the literature that have been used to determine levels of 2-butanone in environmental media and foods at levels that may cause health effects to occur, but they have not been standardized.

6.3.2 On-going Studies

The Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of 2-butanone and other volatile organic compounds in blood, These methods use purge and trap methodology and magnetic sector mass spectrometry which gives detection limits in the low parts per trillion range.

On-going studies involving the development of analytical methods have been identified (EPA 1989b), although no specific information was provided.

7. REGULATIONS AND ADVISORIES

International (World Health Organization) guidelines for 2-butanone were not located. National and state regulations and guidelines pertinent to human exposure to 2-butanone are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to 2-Butanone

Agency	Description	Information	References
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL	200 ppm	OSHA 1989 (29 CFR 1910.0000)
	STEL	300 ppm	
b. Nonspecific media:			
EPA OERR	Reportable quantity	5,000 pounds	EPA 1985a (40 CFR 117 and 302)
Guidelines:			
a. Air:			
ACGIH	TLV TWA	200 ppm	ACGIH 1989
	STEL	300 ppm	
NIOSH	Occupational standard	200 ppm	NIOSH 1978
b: Other:			
EPA	RfD (oral)	$5x10^{-2}$ mg/kg/day	EPA 1989c
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		
Connecticut		11,800 $\mu g/m^3$ (8-hr avg)	NATICH 1988
Kentucky		295 mg/m^3 (8-hr avg)	State of Kentucky 1986
Florida		5.9 mg/m^3 (8-hr avg)	NATICH 1988
Massachusetts		160 $\mu g/m^3$ (24-hr avg)	NATICH 1988
North Carolina		88.5 mg/m^3 (15-min avg)	NATICH 1988
		3.7 mg/m^3 (24-hr avg)	NATICH 1988
North Dakota		5.9 mg/m^3 (8-hr avg)	NATICH 1988
		8.85 mg/m^3 (24-hr avg)	NATICH 1988
Nevada		14.048 mg/m^3 (8-hr avg)	NATICH 1988
New York		1,967 $\mu g/m^3$ (annual)	NATICH 1988
South Carolina		14,750 $\mu g/m^3$ (24-hr avg)	NATICH 1988
South Dakota		11,800 $\mu g/m^3$ (8-hr avg)	NATICH 1988
Virginia		9,800 $\mu g/m^3$ (24-hr avg)	NATICH 1988
b. Water:	Drinking water quality guidelines		
Arizona		170 $\mu g/L$	FSTRAC 1988
Connecticut		1,000 $\mu g/L$	FSTRAC 1988
Massachusetts		350 $\mu g/L$	MAORS 1989
Maine		750 $\mu g/L$	FSTRAC 1988
Minnesota		172 $\mu g/L$	FSTRAC 1988
	Ground water quality standards		
Vermont	Enforcement standard	170 $\mu g/L$	VDEC 1990
	Preventive action limit	85 $\mu g/L$	VDEC 1990

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; NIOSH = National Institute for Occupational Safety and Health; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; RfD = Reference dose; STEL = Short Term Exposure Limit; TLV = Threshold Limit Value; TWA = Time-Weighted Average

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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 (Kd) -- 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.

9. GLOSSARY

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.

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$_{(50)}$ (LC_{50}) -- 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$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ ($LT_{(50)}$) -- 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.

9. GLOSSARY

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

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 *ug*/L for water, mg/kg/day for food, and $\mu g/m^3$ 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 nn a professional judgment of the entire database on the chemical. The RfD 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 bedire.cted 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.

9. GLOSSARY

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.

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 (TD_{50}) -- 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 LOAEL 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-l 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, Minimai 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-l 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-l

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,

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 Freauency/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 exp'osed 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 Wc").

(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 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 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 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/m^3 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 e the LSE table.

(18). Estimated UDDer-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 derive.d 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.

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) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
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)

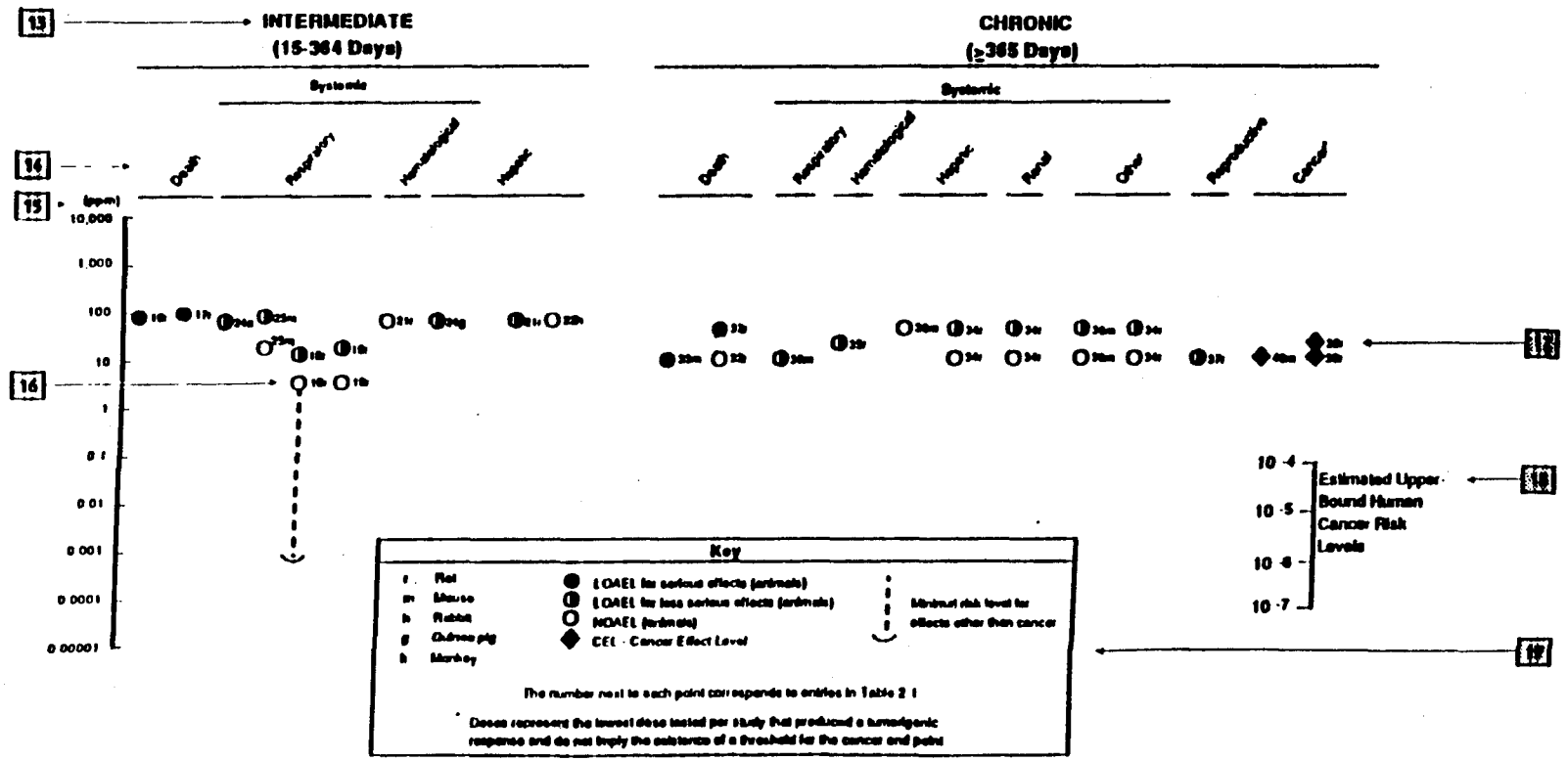

FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

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 aquainthealth 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.

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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 humanhealth 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 continous 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
CERCLA	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
Kd	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

APPENDIX B

LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
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	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States

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UF	uncertainty factor
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	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-butanone. The panel consisted of the following members: Dr. Michael Norvell, Private Consultant, Ringoes, New Jersey; Dr. Rolf Hartung, Department of Environmental and Industrial Health, University of Michigan, Ann Arbor, Michigan; and Dr. Vincent Garry, Director, Laboratory for Environmental Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota. These experts collectively have knowledge of 2-butanone's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. 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.

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