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 2-1 and plotted in Figure 2-1.

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 2-1 and plotted in Figure 2-1.

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 2-1). 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

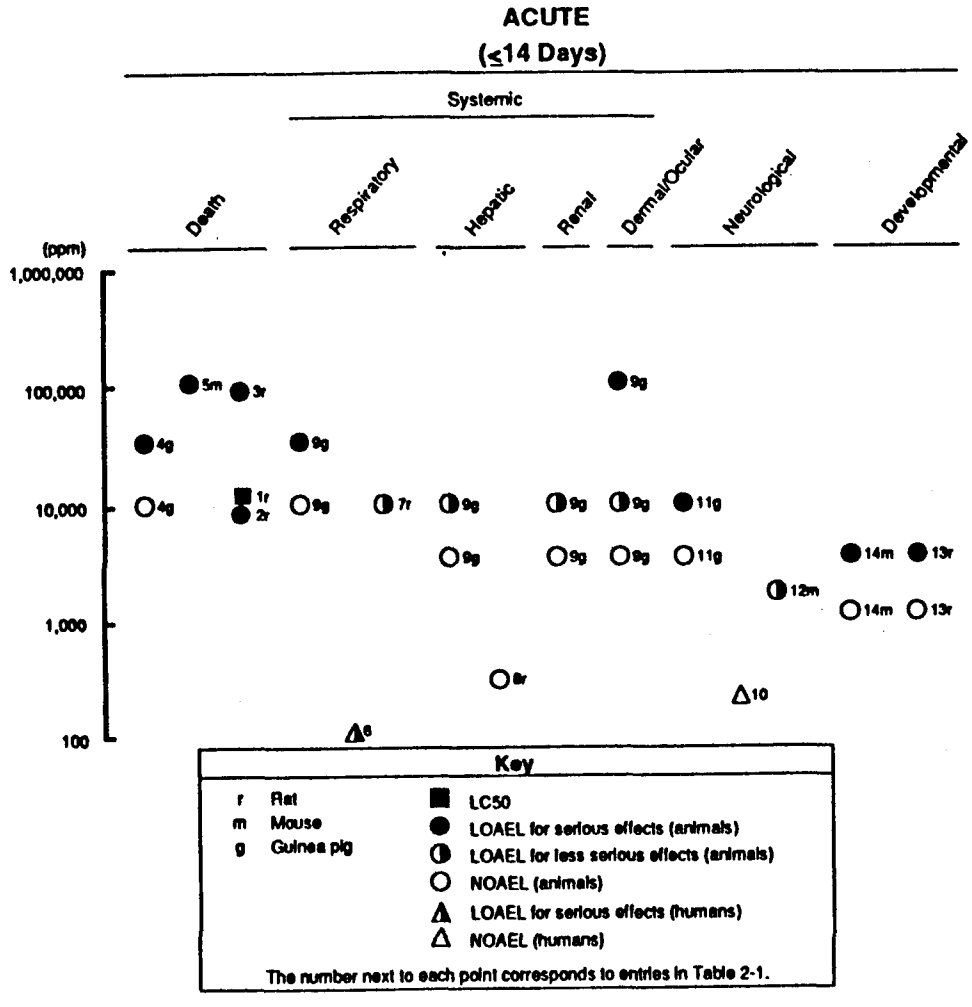
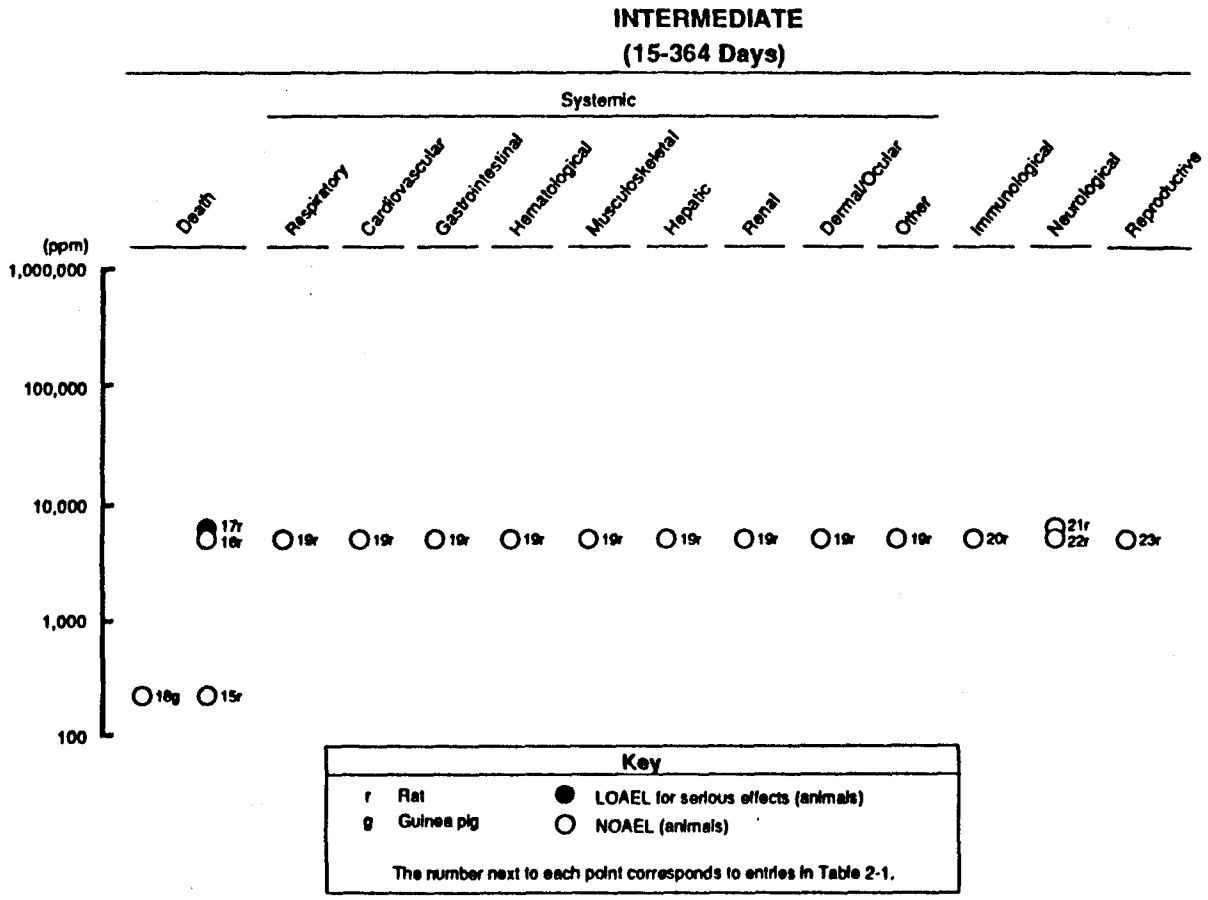


FIGURE 2-1 (Continued)



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

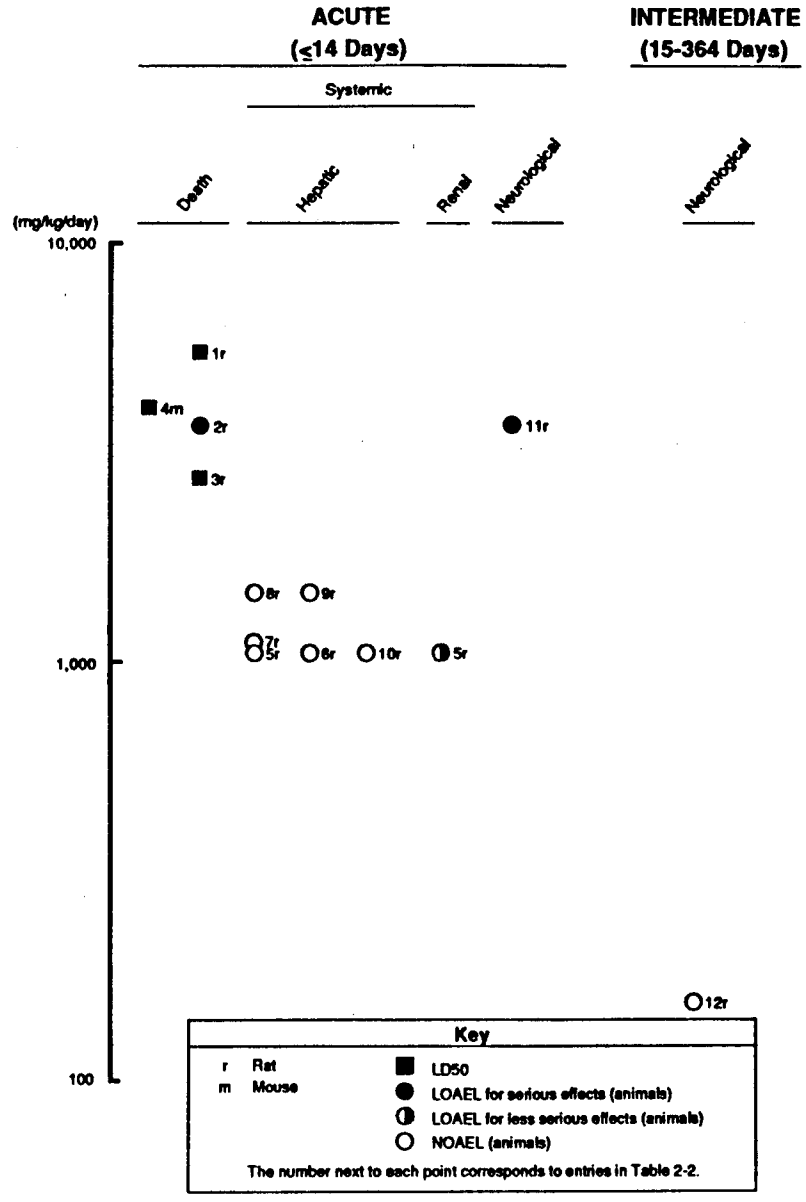
TABLE 2-2 (Continued)

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

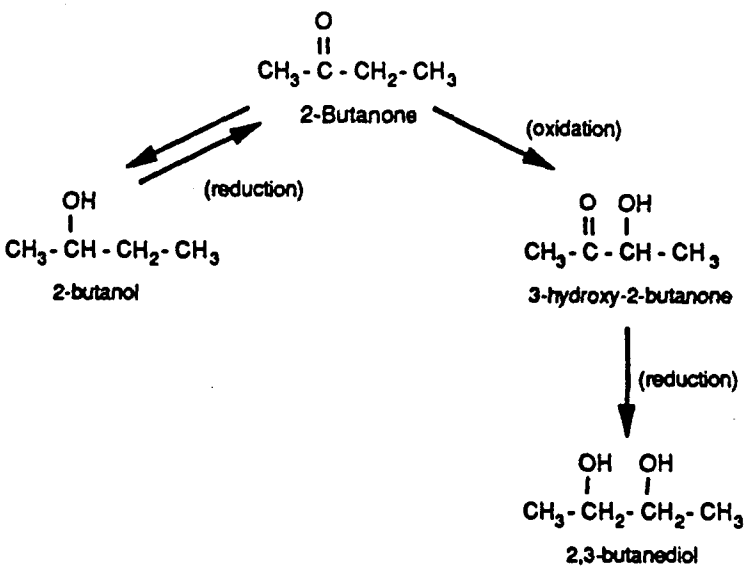
No studies were located regarding the distribution of 2-butanone following dermal exposure in humans or animals.

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.

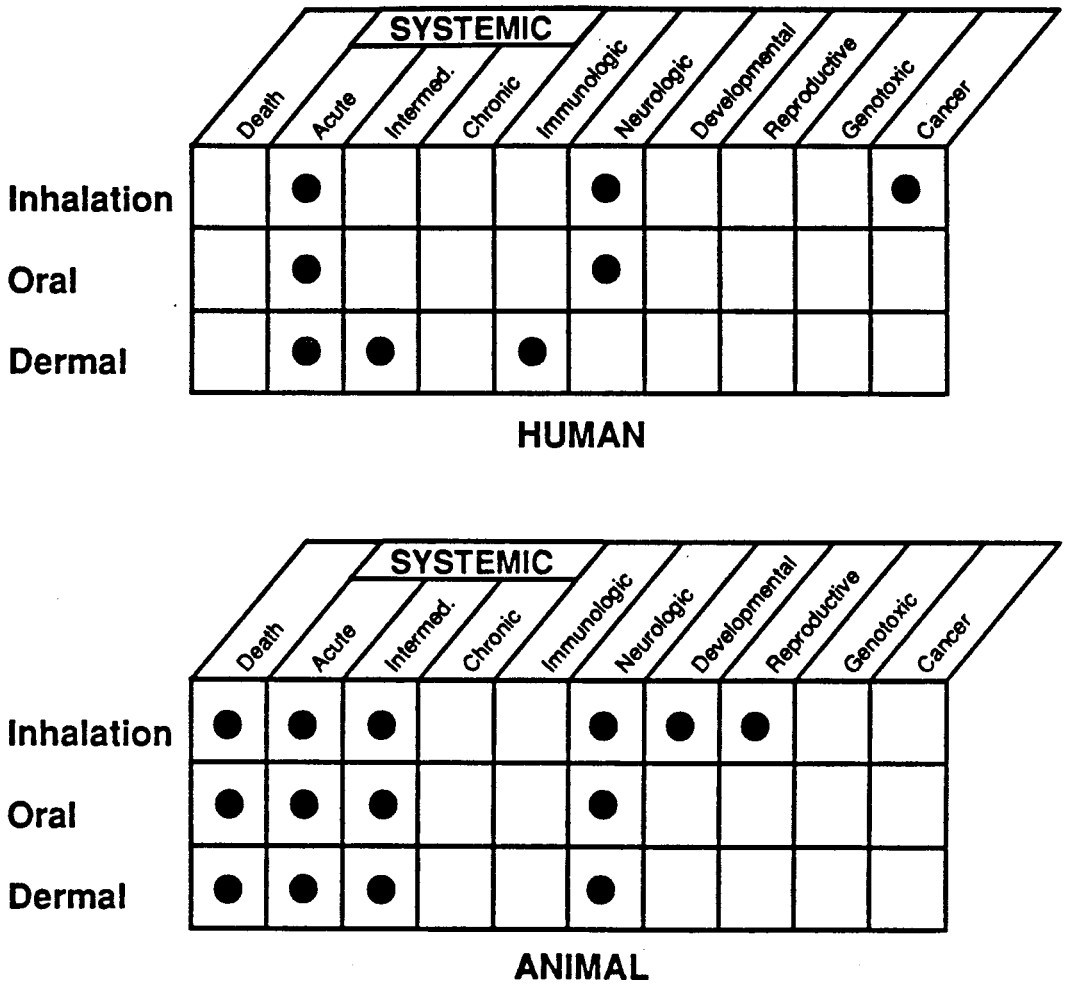
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data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