Toxicological Profile for

ISOPHORONE

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

TOXICOLOGICAL PROFILE FOR ISOPHORONE

Prepared by:

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FOREWORD

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

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

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

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

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

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every 3 years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature that

describes a hazardous substance's toxicological properties. Other literature is presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

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

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public. We plan to revise these documents as additional data become available.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, EPA, the Centers for Disease Control, and the National Toxicology Program. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Walter R. Dowdle, Ph.D.
Acting Administrator
Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS ISOPHORONE?

Isophorone is a clear liquid with a peppermint-like odor. It evaporates faster than water but slower than charcoal starter or paint thinner, and it will not mix completely with water. Isophorone is a man-made chemical for use commercially, but it has been found to occur naturally in cranberries. It is used as a solvent in some printing inks, paints, lacquers, and adhesives. Isophorone does not remain in the air very long, but can remain in water for possibly more than 20 days. The length of time that isophorone will remain in soil is not known, but it probably is about the same as the length of time it remains in water. More information can be found in Chapters 3 and 4.

1.2 HOW MIGHT I BE EXPOSED TO ISOPHORONE?

Exposure to isophorone may take place where you work or in very low concentrations at home. Because it is used in some inks, paints, lacquers, and adhesives, people who work with these products may be exposed to isophorone. Isophorone has been found in the drinking water of Cincinnati, Philadelphia, and New Orleans at amounts less than 10 parts of isophorone in 1 billion parts of water (10 ppb). In one instance (a screen print shop), isophorone was found in amounts as high as 26 parts in 1 million parts of air (26 ppm), but the usual amounts in the workplace are much lower. At this time, isophorone has been found in at least 9 out of 1177 National Priorities List (NPL) hazardous waste sites in the United States. Exposure to isophorone at these sites may occur by touching contaminated soil, water, or sediment. For more information please read Chapter 5.

1.3 HOW CAN ISOPHORONE ENTER AND LEAVE MY BODY?

Isophorone can enter your body if you breathe its vapor, have skin contact with it, drink contaminated water, or eat contaminated food. If isophorone is present at a waste site near homes that use local wells as a source of water, the well water could be contaminated with isophorone. Experiments in animals show that after doses by mouth, isophorone enters easily and spreads to many organs of the body, but most of it leaves the body within 24 hours in the breath and in urine. Isophorone may enter the lungs of workers exposed to isophorone where it is used indoors as a solvent. Isophorone disappears quickly from outside air, so the chance of breathing outdoor air contaminated with isophorone is small. If isophorone is spilled at a waste site and evaporates, however, a person nearby may breathe isophorone before it disappears from the air. In addition, soil around waste sites may contain isophorone, and a person, such as a child playing in the dirt, may eat or have skin contact with the contaminated soil. How much isophorone enters the body through the skin is not known.

More information on how isophorone can enter and leave the body can be found in Chapter 2.

1.4 HOW CAN ISOPHORONE AFFECT MY HEALTH?

The only effects of isophorone reported in humans are irritation of the skin, eyes, nose, and throat, and possibly dizziness and fatigue. These effects have occurred in workers who breathe vapors of isophorone and other solvents during use in the printing industry. Short-term exposure of animals to high vapor amounts and short- or long-term exposure of animals to high doses by mouth cause death or a shortened lifespan. Short-term exposure to high amounts of vapors or high doses by mouth has caused inactivity and coma in animals. Inconclusive studies suggested that isophorone may have caused birth defects and growth retardation in the offspring of rats and mice that breathed the vapors during pregnancy. Some harmful health effects were seen in adult female animals in these studies. It is not known whether isophorone could cause birth defects in humans. In a long-term study in which rats and mice were given high doses of isophorone by mouth, the male rats developed kidney disease and kidney tumors. Male rats also developed tumors in a reproductive gland. Some male mice developed tumors in the liver, in connective tissue, and in lymph glands (tissues of the body that help fight disease), but the evidence was not strong. It is not known whether isophorone causes cancer in humans. More information on the health effects of isophorone in animals and humans can be found in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ISOPHORONE?

No medical test is known to determine human exposure to isophorone. A few studies in rats and rabbits have shown that isophorone and its metabolites can be found in the urine of these animals, so it may be possible to find a method for testing the urine of humans to determine exposure to isophorone. It is not known, however, whether such a measurement would predict how much exposure had occurred or the possible health effects. For more information see Chapter 2.

1.6 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Tables 1-1 through 1-4 show the link between exposure to isophorone and known health effects. A Minimal Risk Level (MRL) is also included in Table 1-3. This MRL was derived from animal data for long-term exposure, as described in Chapter 2 and in Table 2-2. The MRL provides a basis for comparison with levels that people might encounter in food. If a person is exposed to isophorone at an amount below the MRL, it is not expected that harmful (noncancer) health effects will occur. Because this level is based on information that is currently available, some uncertainty is always associated with it. Also, because the method for deriving MRLs does not use any information about cancer, a MRL does not imply anything about the

1. PUBLIC HEALTH STATEMENT

TABLE 1-1. Human Health Effects from Breathing Isophorone*

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects**
25	4 minutes	Eye, nose, throat irritation
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects**
5	1 month	Fatigue, depression

*See Section 1.2 for a discussion of exposures encountered in daily life.

**These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

TABLE 1-2. Animal Health Effects from Breathing Isophorone

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
28	5 minutes	Lung irritation in mice
89	4 hours	Behavior problems in mice
620	6 hours	Lung congestion in rats and mice
885	6 hours	Death in rats
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
37	4 weeks	Poor weight gain in rats
250	18 months	Slight liver effects, eye and nose irritation in rats and rabbits
500	4-6 months	Death in rats

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

TABLE 1-3. Human Health Effects from Eating or Drinking Isophorone*

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from short-term human exposure to food containing specific levels of isophorone are not known.
Levels in Water (ppm)		The health effects resulting from short-term human exposure to water containing specific levels of isophorone are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
7		Minimal risk level (based on animal data, see Section 1.6 for discussion)
Levels in Water (ppm)		The health effects resulting from long-term human exposure to water containing specific levels of isophorone are not known.

*See Section 1.2 for a discussion of exposures encountered in daily life.

TABLE 1-4. Animal Health Effects from Eating or Drinking Isophorone

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects*
8000	1 day	Fatigue, staggering in mice
Levels in Water (ppm)		
11,000	1 day	Death in mice
15,000	1 day	Death in rats
Long-term Exposure (greater than 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects*
1900	2 years	Liver disease, stomach irritation in mice
5000	2 years	Kidney disease in rats
8000	13 weeks	Death in mice
15,000	16 days	Death in mice
Levels in Water (ppm)		
		The health effects resulting from long term animal exposure to drinking water containing specific levels of isophorone are not known.

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

presence, absence, or level of risk of cancer. The information on health effects in humans or animals for short-term or long-term exposure to isophorone in air, for short-term exposure in food or water, and for long-term exposure in water was either not available or not suitable to derive MRLs.

The amounts listed in Table 1-1 that cause eye, nose, and throat irritation (25 ppm) with short-term exposure and fatigue and depression (5 ppm) with long-term exposure are much higher than the amount at which the odor is first noticed, which is about 0.2 ppm. This means that you can probably smell isophorone before you would have harmful health effects. The levels of isophorone in air that cause death and lung congestion in animals are much higher than the amounts that workers breathe in industry when using isophorone as a solvent. The amount that causes lung irritation in animals is about the same as the amount that causes eye, nose, and throat irritation in humans.

Besides the harmful health effects from exposure to isophorone in air, food, and water, skin irritation or eye damage occurred in animals after a few drops of isophorone had been applied directly to the skin or eyes.

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

The Environmental Protection Agency (EPA) has determined that the level of isophorone in natural waters (lakes, streams) should be limited to 5.2 parts isophorone per million parts of water (5.2 ppm) to protect human health from the harmful effects of isophorone from drinking the water and from eating contaminated fish and other animals found in the water. The Occupational Safety and Health Administration (OSHA) has set a permissible exposure limit of 4 parts of isophorone per million parts of workroom air (4 ppm) during an 8-hour work shift to protect workers. The National Institute for Occupational Safety and Health (NIOSH) recommends that the amount in workroom air be limited to 4 ppm averaged over a 10-hour work shift. Further information on government recommendations can be found in Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have more questions or concerns, please contact your State Health or Environmental Department or:

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

2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to isophorone. Its purpose is to present levels of significant exposure for isophorone based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of isophorone and (2) a depiction of significant exposure levels associated with various adverse health effects.

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 data in this section are 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, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) 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, determine whether or not the intensity of the effects varies 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 on the tables and graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious effects." Public health officials and project managers concerned with response actions at Superfund 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) are of interest to health professionals and citizens alike.

2. HEALTH EFFECTS

For certain chemicals, levels of exposure associated with carcinogenic effects may be indicated in the figures. These levels reflect the actual doses associated with the tumor incidences reported in the studies cited. Because cancer effects could occur at lower exposure levels, the figures also show estimated excess risks, ranging from a risk of one in 10,000 to one in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1980a), uncertainties are associated with the techniques.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding death of humans following inhalation exposure to isophorone.

Acute inhalation exposure of rats, guinea pigs, or mice to isophorone at a concentration of 619 ppm for 6 hours caused slight lacrimation during exposure but did not result in any deaths (Hazleton Labs 1964). Although this study used few animals and did not report the use of controls, the acute exposure level of 619 ppm probably can be considered a NOAEL for lethality because none of the animals of the three species tested died (Table 2-1 and Figure 2-1). Hazleton Labs (1965a) statistically determined the 4-hour LC_{50} in rats to be 1238 ppm, with 95% confidence limits of 1008-1531 ppm. The LC_{50} is indicated in Table 2-1 and Figure 2-1. Exposure to 885 ppm for 6 hours resulted in the death of 1/10 rats (Hazleton Labs 1965a); the exposure of 885 ppm is considered the acute inhalation LOAEL for lethality of isophorone (see Table 2-1 and Figure 2-1). The concentration of 885 ppm in air (Hazleton Labs 1965a) is also presented in Table 1-2. The cause of death of the rats was not stated, but marked pulmonary congestion was observed. Dutertre-Catella (1976) attempted to determine the LC_{50} of isophorone in rats and rabbits, but saturation of the air at a concentration up to 7000 ppm for 5 hours produced mortality in only 10% of the rats and 30% of the rabbits. The animals became comatose before death and had hemorrhagic lungs, vascular dilation of the alveolar capillaries and peribronchial vessels. Dutertre-Catella (1976) noted that at high concentrations of vapor, which were attained by heating isophorone, an appreciable quantity of the solvent remained suspended as an aerosol in the exposure chamber due to condensation. As the concentrations at which the animals began to die could not be determined from the report, the LOAELs are not known.

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

Graph Key	Species	Exposure Frequency/ Duration	Effect	NOAEL[b] (ppm)	LOAEL[a] (Effect) Less Serious (ppm)	LOAEL[a] (Effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	rat	once 6 hr		619			Hazleton Labs 1964
2	rat	once 4 hr				1238 (LC_{50})	Hazleton Labs 1965a
3						885 (1/10 died)	
4	mouse	once 6 hr		619			Hazleton Labs 1964
5	guinea pig	once 6 hr		619			Hazleton Labs 1964
Systemic							
6,7	human	15 min	Dermal/ Ocular	10	25 (irritation)		Silverman etal. 1946
8,9	human	7 min	Dermal/ Ocular	18	35 (eye irritation) (throat irritation)		Hazleton Labs 1965b
10	rat	once 6 hr	Respiratory		619 (congestion)		Hazleton Labs 1964
11	mouse	5 min	Respiratory		27.8 (RD_{50})		DeCeaurriz et al. 1981a
12	mouse	once 6 hr	Respiratory		619 (congestion)		Hazleton Labs 1964
Neurological							
13	rat	once 4 hr				1238 (comatose)	Hazleton Labs 1965a
14	mouse	4 hr			89 (behavioral test)		De Ceaurriz et al. 1984
15	mouse	once 4 hr			131 (CNS depression)		De Ceaurriz et al. 1981b

TABLE 2-1 (continued)

Graph Key	Species	Exposure Frequency/ Duration	Effect	NOAEL[b] (ppm)	LOAEL[a] (Effect) Less Serious (ppm)	LOAEL[a] (Effect) Serious (ppm)	Reference
Developmental							
16 17 18	rat	9 d d 6-15gestation 6 hr/d		100		115 (growth retardation) 150 (exencephaly)	Bio/dynamics 1984a,b
19,20	mouse	9 d d 6-15gestation 6 hr/d		115		150 (exencephaly)	Bio/dynamics 1984a,b
INTERMEDIATE EXPOSURE							
Death							
21	rat	4-6 mo 6 hr/d 5 d/wk				500 (1/10 F, 3/10 M died)	Dutertre-Catella 1976
Systemic							
22 23 24	rat	4 wk 6 hr/d 5 d/wk	Hematological Renal Other	37 37	37 (decreased body weight gain)		Hazleton Labs 1968
25 26 27	rat	4-6 mo 6 hr/d 5 d/wk	Respiratory Hepatic Dermal/ Ocular	500 500	500 (ocular and nasal irritation)		Dutertre-Catella 1976
Neurological							
28,29	human	1 mo		1-4	5-8 (fatigue) (malaise)		Ware 1973
CHRONIC EXPSOSURE							
Death							
30	rat	18 mo 6 hr/d 5 d/wk		250			Dutertre-Catella 1976

TABLE 2-1 (continued)

Graph Key	Species	Exposure Frequency/ Duration	Effect	NOAEL[b] (ppm)	LOAEL[a] (Effect) Less Serious (ppm)	LOAEL[a] (Effect) Serious (ppm)	Reference
31	rabbit	18 mo 6 hr/d 5 d/wk		250			Dutertre-Catella 1976
Systemic							
32	rat	18 mo	Respiratory	250			Dutertre-Catella 1976
33		6 hr/d	Hematological	250			
34		5 d/wk	Hepatic		250 (microvacuolization)		
35			Renal	250			
36			Dermal/ Ocular		(irritation of nasal mucosa)		
37	rabbit	18 mo	Respiratory	250			Dutertre-Catella 1976
38		6 hr/d	Hematological	250			
39		5 d/wk	Hepatic		250 (microvacuolization)		
40			Renal	250			
41			Dermal/ Ocular		250 (irritation of nasal mucosa)		

[a]LOAEL - Lowest Observed Adverse Effect Level
[b]NOAEL - No Observed Adverse Effect Level

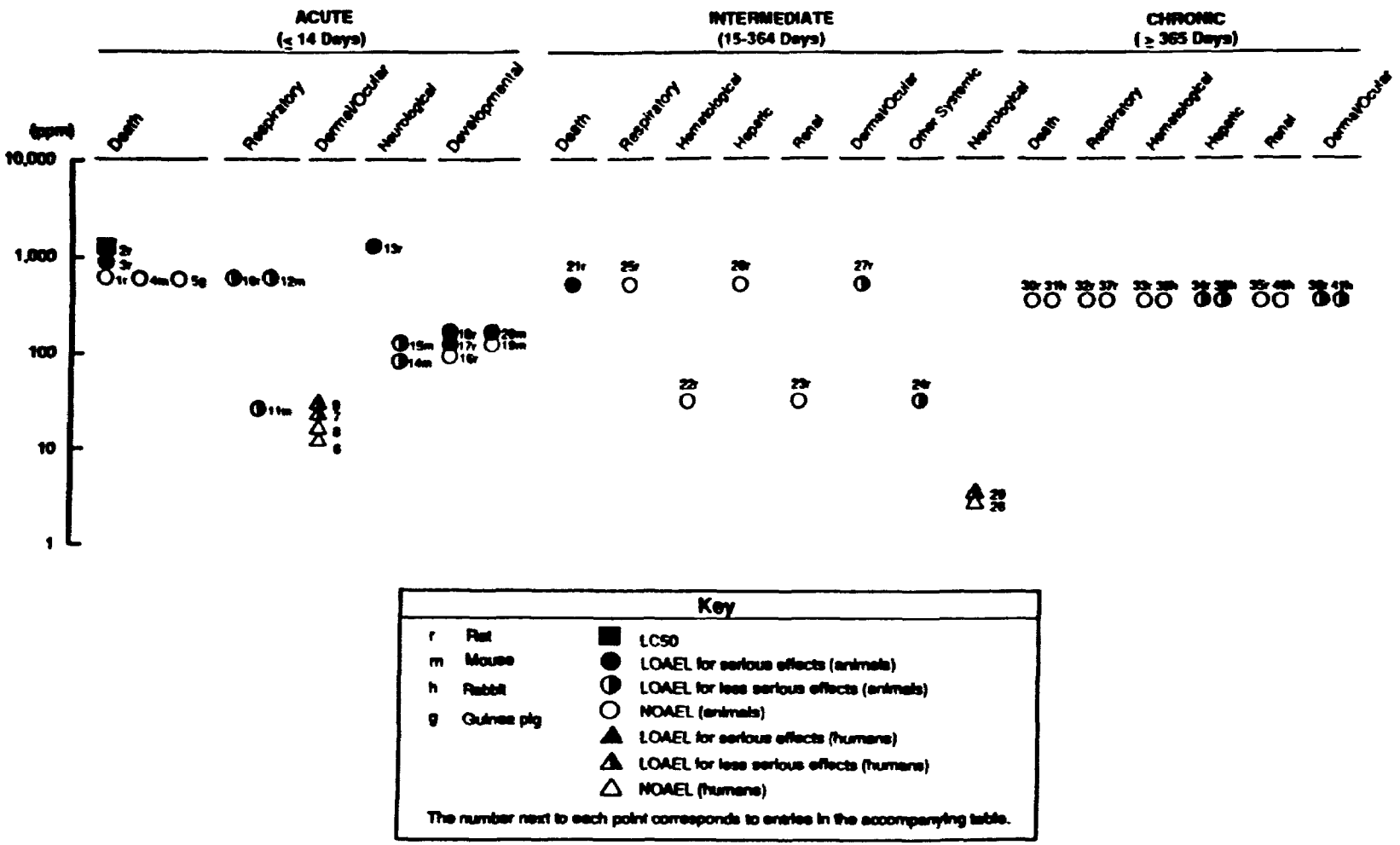


FIGURE 2-1. Levels of Significant Exposure to Isophorone - Inhalation

In an intermediate duration study, 1/10 female rats and 3/10 male rats died after being exposed to 500 ppm isophorone for 6 hours/day for up to 6 months (Dutertre-Catella 1976). The 500 ppm concentration is presented in Table 2-1 and plotted in Figure 2-1 as the intermediate duration LOAEL for lethality. The concentration of 500 ppm (Dutertre-Catella 1976) is also presented in Table 1-2. No differences in mortality were observed in rats compared with controls, and no deaths occurred in rabbits exposed to 250 ppm isophorone, 6 hours/day for 18 months (Dutertre-Catella 1976). The 250 ppm concentration is a chronic inhalation NOAEL for lethality in both rats and rabbits (see Table 2-1 and Figure 2-1).

2.2.1.2 Systemic Effects

Respiratory Effects. Lee and Frederick (1981) found that eye, respiratory, and skin irritation were among the complaints of 27/35 workers in a printing plant. Two of the workers (screen printers) were exposed to 8-hour TWA concentrations of isophorone of 0.7 and 14 ppm, but it was not clear whether these two individuals were among those who complained of respiratory irritation. Lee and Frederick (1981) concluded that screen printers are exposed to hazardous concentrations of isophorone and other solvents (xylene, methylene chloride, and toluene).

Very little information is available concerning the systemic effects on the respiratory system of animals due to inhalation exposure to isophorone. Isophorone is irritating to the respiratory tract of animals. DeCeaurriz et al. (1981a) reported that a concentration of 27.8 ppm for 5 minutes caused a 50% decrease (RD_{50}) in the reflex respiratory rate of mice, an indication of respiratory irritation. Because the lowest concentration resulting in a decreased respiratory rate was not indicated clearly in the study, the 27.8 ppm level is indicated as a LOAEL for less serious respiratory effects in mice due to acute inhalation exposure to isophorone (see Table 2-1 and Figure 2-1).

Slight lung congestion was observed in rats and mice sacrificed immediately after exposure to 619 ppm isophorone for 6 hours, but not in rats or mice sacrificed 14 days after the exposure (Hazleton Labs 1964), suggesting reversibility of the lesion. This study used only one concentration (619 ppm) and did not report the use of controls. Nevertheless, isophorone is known to be irritating to mucous membranes (see Dermal/Ocular effects below), so it is reasonable to attribute the lung congestion to exposure to isophorone. As the congestion was not a permanent condition, it is not a serious adverse effect; therefore, the 619 ppm level is indicated in Table 2-1 and Figure 2-1 as a LOAEL for less serious effects on the respiratory system due to acute inhalation exposure to isophorone. Rats and rabbits that were exposed to isophorone at concentrations up to 7000 ppm for 5 hours died and had hemorrhagic lungs with vascular dilation of the alveolar capillaries and peribronchial vessels (Dutertre-Catella 1976). The concentration of 7000 ppm cannot be considered a LOAEL because it was not clear from the report if the animals started dying at

concentrations less than 7000 ppm. Moreover, Dutertre-Catella (1976) noted that at 7000 ppm, a considerable quantity of the isophorone was present in the exposure atmosphere as an aerosol rather than as a vapor. The concentration of 27.8 ppm in air (DeCeaurriz et al. 1981a) was rounded to 28 ppm, and the concentration of 619 ppm in air was rounded to 620 ppm (Hazleton Labs 1964) for presentation in Table 1-2.

Severe lung injury consisting of congestion, necrosis, and degeneration was reported in rats and guinea pigs exposed intermittently to 100 ppm, but not to 25 ppm, isophorone for 6 weeks (Smyth et al. 1942). According to Rowe and Wolf (1963), however, later investigation led to the conclusion that the isophorone used by Smyth et al. (1942) contained several highly volatile impurities, a fact unknown to the investigators at the time. These impurities could have contributed to the severity of the observed effects. Moreover, Rowe and Wolf (1963) argued that some of the vapor concentrations reported by Smyth et al. (1942) were higher than could possibly be achieved under the conditions employed and some were overestimated because the vapor concentrations of the impure commercial product within the exposure chamber were determined using an interferometer that had been calibrated against pure isophorone.

These criticisms of the Smyth et al. (1942) study have also been noted by NTP (1986) and ACGIH (1986). Given the uncertainty regarding the results and the exposure levels reported by Smyth et al. (1942), it is inappropriate to consider this study for the determination of levels of significant exposure.

Hazleton Labs (1968) found no treatment-related histopathological lesions in lungs of rats exposed intermittently to 37 ppm for 4 weeks compared with controls. The 37 ppm concentration was the only one tested, and histological examination was limited to 30% of the control and treated rats. Although the limited histological examination could have missed lung lesions in the rats that were not examined (70%), no exposure-related histopathological lesions were observed in the lungs of rats exposed to 500 ppm isophorone for up to 6 months or in rats and rabbits exposed to 250 ppm for 18 months (Dutertre-Catella 1976). The NOAELs for respiratory effects of 500 ppm in rats for intermediate duration exposure and 250 ppm in rats and rabbits for chronic exposure are presented in Table 2-1 and Figure 2-1.

Hematological Effects. No studies were located regarding hematological effects in humans following inhalation exposure to isophorone.

Hematological effects of inhalation exposure of animals to isophorone are not well documented. No studies were located regarding hematological effects in animals following acute inhalation exposure to isophorone. Hazleton Labs (1968) compared the hematological effects of inhalation exposure to isophorone with those of three other ketones in rats. The post-exposure values in the treated and control groups were compared with the

pre-exposure values. No extreme variations occurred in any group, but the isophorone-exposed group (37 ppm for 4 weeks) had an increased percentage of lymphocytes (3% in males, 5.8% in females), decreased percentage of neutrophils (2.8% in males, 5.0% in females), and increased hemoglobin content (1.2-1.4 g/100 ml) compared with the pre-exposure values. Since statistical analysis was not performed, the significance of these findings is not known. The control males also displayed this trend. Because the variations in the isophorone-treated group were slight, and similar to those observed in the unexposed animals, the 37 ppm concentration can be considered a NOAEL for hematological effects of intermediate duration inhalation exposure to isophorone. No exposure-related hematological effects were observed in rats or rabbits exposed to 250 ppm isophorone for 18 months (Dutertre-Catella 1976), which is a NOAEL for chronic exposure. The NOAELs are presented in Table 2-1 and Figure 2-1.

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

No studies were located regarding hepatic effects in animals following acute inhalation exposure to isophorone. In the Hazleton Labs (1968) 4-week study, rats exposed to 37 ppm had statistically significant decreased mean absolute liver weights and statistically significant decreased mean liver-to-body weight ratios compared with controls. Histological examination of the livers of 30% of the rats revealed no treatment-related liver lesions; therefore, the toxicological significance of the decreased liver weight is probably minimal. As 70% of the rats in each group were not examined histologically, however, the possibility exists that histopathological liver lesions were missed. No exposure-related histopathological liver lesions occurred in rats exposed to 500 ppm isophorone for up to 6 months, but cytoplasmic microvacuolization of hepatocytes was observed in rats and rabbits exposed to 250 ppm isophorone for 18 months (Dutertre-Catella 1976). The NOAEL of 500 ppm for intermediate duration exposure and the LOAEL of 250 ppm for chronic exposure are presented in Table 2-1 and Figure 2-1. The concentration of 500 ppm in air (Dutertre-Catella 1976) is also presented in Table 1-2.

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

No studies were located regarding kidney effects in animals following acute inhalation exposure to isophorone. Smyth et al. (1942) found severe kidney damage, consisting of congestion, necrosis, and degeneration, in rats and guinea pigs exposed intermittently to 100 ppm isophorone for 6 weeks. As noted, however, Rowe and Wolf (1963) criticized this study for using impure isophorone and overestimating the exposure concentrations. Therefore the 100 ppm level cannot be considered the LOAEL for serious effects on the kidney due to inhalation exposure to isophorone.

In the Hazleton Labs (1968) 4-week study, no treatment-related histopathological effects on the kidney were found in rats exposed to 37 ppm. Because the histological examination was performed on only 30% of the treated and control rats, however, the possibility exists that renal lesions were missed. The 37 ppm concentration can be considered an intermediate duration NOAEL for kidney effects, however, because no exposure-related renal effects were detected upon urinalysis and histological examination of rats and rabbits that were exposed to isophorone in air at a concentration of 250 ppm for 18 months (Dutertre-Catella 1976). The NOAELs of 37 ppm for intermediate duration and 250 ppm for chronic exposure are presented in Table 2-1 and Figure 2-1.

Dermal/Ocular Effects. Isophorone is irritating to the eyes and mucous membranes of humans. Several studies have attempted to determine the thresholds for eye, nose, and throat irritation for isophorone in humans. As seen from Table 2-1, when the exposure duration was 15 minutes, 10 ppm was tolerated, while 25 ppm produced irritation to the eye, nose, and throat (Silverman et al. 1946). NIOSH (1978a) noted that Silverman et al. (1946) did not discuss acclimatization. In another study, when the exposure duration was 7 minutes, no irritation was reported at 18 ppm, but the threshold for throat irritation was 35 ppm. Eye and nose irritation occurred at 65 ppm, but not at 35 ppm (Hazleton Labs 1965b). Since no exposure concentrations between 35 and 65 ppm were tested, the threshold for eye and nose irritation falls between these concentrations. The subjects were retested after 2 weeks, with no significant difference between the trials. Thus, these thresholds appear to be reliable, although there was some concern that the concentrations were slightly overestimated because the isophorone may not have vaporized completely. Furthermore, only six subjects per group were tested, and there was substantial individual variability in response. Smyth and Seaton (1940) reported that exposure of humans for a few minutes to 40-400 ppm resulted in eye, nose, and throat irritation at all exposures, but Rowe and Wolf (1963) criticized this study for using impure isophorone and overestimating the exposure concentrations. The NOAELs and LOAELs for irritation due to 7 and 15 minutes of exposure in the studies by Silverman et al. (1946) and Hazleton Labs (1965b) are indicated in Table 2-1 and Figure 2-1. The concentration of 25 ppm in air (Silverman et al. 1946) is presented in Table 1-1.

The irritancy properties of isophorone have also been observed in humans exposed occupationally to isophorone. In an industrial hygiene survey, Kominsky (1981) reported that the eye and nose irritation complained of by a screen printer could have been caused by 4-minute exposure to 25.7 ppm isophorone, which was measured in the personal breathing zone while the worker was washing a screen. Lee and Frederick (1981) found that eye, respiratory, and skin irritation were among the complaints of 27/35 workers in a printing plant where isophorone and other solvents (xylene, methylene chloride, and toluene) were used. On the day of measurement, two of the screen printers were found to be exposed to 8-hour TWA concentrations of isophorone of 0.7 and 14 ppm, but it was not clear

whether these two individuals were among the workers complaining of irritation. The odor threshold for isophorone in air has been reported to be 0.2 ppm (v/v) (Amoore and Hautala 1983).

Isophorone is also irritating to animals. Smyth et al. (1942) reported conjunctivitis and skin irritation in rats and guinea pigs exposed to isophorone at high concentrations; as discussed above, however, Rowe and Wolf (1963) criticized this study for using impure isophorone and for overestimating the exposure concentrations. As discussed above for respiratory effects, a concentration of 27.8 ppm for 5 minutes caused a 50% decrease (RD_{50}) in the reflex respiratory rate of mice, which indicated sensory irritation rather than a neurological effect (DeCeaurriz et al. 1981a). Irritation of the eyes and nasal mucosa was observed in rats exposed to 500 ppm isophorone in air for up to 6 months and rats and rabbits exposed to 250 ppm for 18 months (Dutertre-Catella 1976). These LOAELs for intermediate and chronic duration exposure are presented in Table 2-1 and Figure 2-1. The 250 ppm concentration is also presented in Table 1-2.

Other Systemic Effects. In the 4-week Hazleton Labs (1968) study, exposure of rats to 37 ppm resulted in statistically significant decreased body weight gain. The 37 ppm level can be considered a LOAEL for less serious effects for intermediate inhalation exposure to isophorone (see Table 2-1 and Figure 2-1). The concentration of 37 ppm in air is presented in Table 1-2.

2.2.1.3 Immunological Effects

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

2.2.1.4 Neurological Effects

Isophorone affects the central nervous system. In an industrial hygiene survey report, Lee and Frederick (1981) attributed dizziness complained of by workers to exposure to isophorone and other solvents (xylene, toluene, methylene chloride). In a communication to the American Conference of Governmental Industrial Hygienists, Ware (1973) reported that employees exposed for 1 month to 5-8 ppm isophorone complained of fatigue and malaise. Complaints stopped when workroom exposure levels of isophorone were lowered to 1-4 ppm. This communication formed the basis for establishing the ACGIH Ceiling Limit of 5 ppm for isophorone (ACGIH 1986). Thus, 5 ppm can be considered a LOAEL and the range of 1-4 ppm a NOAEL for neurological effects in humans due to intermediate inhalation exposure to isophorone (see Table 2-1 and Figure 2-1). The concentration of 5 ppm in air (Ware 1973) is presented in Table 1-1.

Neurological effects of inhalation exposure to isophorone also have been reported in animals. Narcosis and ataxia occurred in rats and guinea pigs at high exposure concentrations for 6-24 hours (Smyth and Seaton 1940),

but Rowe and Wolf (1963) noted that this study used impure isophorone and overestimated the concentrations. DeCeaurriz et al. (1984) found dose-related neurobehavioral effects (decreased immobility in a behavioral despair swimming test) in mice exposed for 4 hours. The lowest concentration resulting in the behavioral effects was 89 ppm, which is indicated as a less serious LOAEL in Table 2-1 and Figure 2-1. The concentration of 89 ppm in air (DeCeaurriz et al. 1984) is presented in Table 1-2.

DeCeaurriz et al. (1981b) also reported that inhalation of isophorone for 4 hours by mice increased the threshold for onset of seizures produced by intravenous administration of pentrazole, indicating that isophorone depressed the central nervous system. The concentration of isophorone that resulted in a 50% increase in the seizure threshold (STI_{50}) was 131 ppm (LOAEL for less serious effects on Table 2-1 and Figure 2-1), with 95% confidence intervals of 113-145 ppm. At the 4-hour LC_{50} of 1238 ppm and higher, rats were ataxic and comatose during exposure, after which they displayed depression and inactivity (Hazleton Labs 1965a). The 1238 ppm concentration is indicated as a LOAEL for serious effects in Table 2-1 and Figure 2-1. These effects were not noted at 885 ppm. Although the exposure concentration of 885 ppm did not result in overt signs of neurotoxicity, more sensitive tests for neurotoxicity (e.g., operant performance, motor activity, electrophysiology), which may have revealed neurobehavioral effects at this level, were not performed. Therefore, the concentration of 885 ppm should not be considered a NOAEL for neurotoxicity for acute inhalation exposure. Rats and rabbits that were exposed to isophorone for 5 hours at concentrations up to 7000 ppm became comatose and died (Dutertre-Catella 1976). The concentration of 7000 ppm cannot be considered a LOAEL because it was not clear from the report whether the animals became comatose at concentrations less than 7000 ppm. Furthermore, at high concentrations, a considerable amount of isophorone was present in the exposure atmosphere as an aerosol rather than as a vapor (Dutertre-Catella 1976).

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans following inhalation exposure to isophorone.

As part of an intermediate duration study, in which rats were exposed to 500 ppm isophorone in air, Dutertre-Catella (1976) mated exposed males with exposed females, control males with exposed females, exposed males with control females, and control males with control females after 3 months of exposure. Exposure of females continued throughout gestation, and they were allowed to deliver. No differences in pregnancy rate or litter size and no abnormalities in pups were found. The pups were not examined for internal malformations; therefore, this study was inadequate to determine developmental effects of isophorone.

In a pilot developmental toxicity study, pregnant rats and mice were exposed by inhalation to isophorone at concentrations up to 150 ppm on days 6-15 of gestation (Bio/dynamics 1984a). Dose-related mild maternal toxicity (increased liver weight and clinical signs) occurred at all concentrations (≥50 ppm) in rats, but there was no clear indication of maternal toxicity in mice. Exencephaly was observed in one late resorption in one litter in the high-concentration group of rats, and in one late resorption in one litter and in two live fetuses in another litter in the high-concentration group of mice. Because this was a pilot study, only 12 female rats and 12 female mice were used, and the fetuses were examined only for gross abnormalities. A second, more complete developmental toxicity study was also performed in two species. Groups of 22 female rats and 22 female mice were exposed on gestation days 6-15 to concentrations of isophorone up to 115 ppm (Bio/dynamics 1984b). In rats, dose-related maternal toxicity (alopecia) was seen at all concentrations (≥25 ppm). In addition, rat dams exposed to 115 ppm had lower body weights than controls on some days. No other indications of maternal toxicity were noted. There was a statistically significant reduction in mean crown-rump length among rat fetuses, but not among litters, in the group exposed to 115 ppm. In mice, the only effect noted was that the mean body weight of dams exposed to 115 ppm isophorone was decreased during one day of the treatment period. Bio/dynamics (1984b) concluded that isophorone was not teratogenic or fetotoxic in rats or mice at concentrations up to 115 ppm. This conclusion is not supported by the results. Although significance across litters was not reached, the reduction in crown-rump length in the offspring of rats exposed to 115 ppm is evidence of growth retardation. Several deviations from the protocol resulted in the failure to perform some of the scheduled fetal examinations. Bio/dynamics (1984b) stated that these deviations did not alter the conclusions. Based on the findings of the second study, Bio/dynamics (1984b) did not regard the occurrences of exencephaly in the pilot study to be treatment-related. This conclusion is untenable because the second study did not test isophorone at 150 ppm, the exposure level at which the exencephaly was observed. Thus, the findings in the pilot study are difficult to interpret; the incidences of exencephaly/litter at the 150 ppm exposure were not significantly different from controls, but this malformation was observed only at the 150 ppm exposure level. Furthermore, the malformation was seen in both species. Although these results are inconclusive, 150 ppm may be a serious LOAEL for malformations in rats and mice, and 115 ppm may be a NOAEL in mice. The concentration of 115 ppm in rats, however, was associated with growth retardation and represents a serious LOAEL for developmental effects of inhalation exposure. The NOAEL for rats is 100 ppm, which was the next lower dose in the Bio/dynamics (1984a,b) studies. The NOAELs and LOAELs are indicated in Table 2-1 and Figure 2-1.

2.2.1.6 Reproductive Effects

As discussed above in Section 2.2.1.5, no differences in pregnancy rate or litter size were observed in rats exposed to isophorone in air at 500 ppm

for 3 months before mating (Dutertre-Catella 1976). Since this study did not examine other parameters of reproductive toxicity, 500 ppm cannot be considered a NOAEL for reproductive effects.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following inhalation exposure to isophorone.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals following inhalation exposure to isophorone.

2.2.2 Oral Exposure

No studies were located regarding health effects in humans following oral exposure to isophorone.

2.2.2.1 Death

The oral LD_{50} of isophorone was reported as 3450 mg/kg in male rats (Hazleton Labs 1964) and 2104-2150 mg/kg in female rats (Smyth et al. 1969, 1970). LD_{50} values of 2700 ± 200 mg/kg for male rats, 2100 ± 200 mg/kg for female rats, and 2200 ± 200 mg/kg for male mice also were reported by Dutertre-Catella (1976). The value reported by Hazleton Labs (1964) was estimated because the mortality data did not lend itself to statistical analysis. Furthermore, the doses were widely spaced, and the animals were fasted for only 3-4 hours before dosing, which could have interfered with gastrointestinal absorption of isophorone. Necropsy of rats that died revealed congestion of the lungs, kidneys, adrenals, and pancreas, and gastrointestinal inflammation. Necropsy of rats that survived the 14-day observation period revealed no effects. The studies by Smyth et al. (1969, 1970) were determinations of the joint toxic action of 27 pairs of industrial solvents (see Section 2.7 on Interactions with other chemicals), but the details of the individual LD_{50} determinations and the cause of death were not provided. Nevertheless, the values for isophorone were reproducible in the two studies by Smyth et al. (1969, 1970). The reason for the sex difference is not apparent. The LD_{50}s are indicated in Table 2-2 and Figure 2-2. No short-term studies of isophorone administered in food or drinking water were located. The LD_{50} of ≈2100 mg/kg, which was determined using liquid isophorone by gavage (Smyth et al. 1969, 1970), was converted to an equivalent concentration of 15,000 ppm in water for presentation in Table 1-4.

Lethality data for intermediate duration oral exposure to isophorone are provided for 16 days and for 13 weeks of exposure in the NTP (1986) study. For the 16-day experiment, Table 2-2 and Figure 2-2 indicate 2000 mg/kg/day as a LOAEL for lethality and 1000 mg/kg/day as a NOAEL for

Table 2-2. Levels of Significant Exposure to Isophorone - Oral

Graph Key	Species	Route[a]	Exposure Frequency/ Duration	Effect	NOAEL[b]	LOAEL[c] (Effect) Less Serious (mg/kg/day)	LOAEL[c] (Effect) Serious	Reference
ACUTE EXPOSURE								
Death								
1	rat	(G)	once				2104- 2150 (LD_{50})	Smyth et al. 1969,1970
2,3	rat	(G)	once		1450		3450 (estimated LD_{50})	Hazleton Labs 1964
4	mouse	(G)	once				2200 (LD_{50})	Dutertre-Catella 1976
Neurological								
5,6	rat	(G)	once			1450 (depression)	5000 (prostration)	Hazleton Labs 1964
INTERMEDIATE EXPOSURE								
Death								
7,8	rat	(G)	16 d 5 d/wk (12 doses in 16 d)		1000		2000 (4/5F died) (1/5M died)	NTP 1986
9,10	mouse	(G)	16 d 5 d/wk (12 doses in 16 d)		1000		2000 (100% mort)	NTP 1986
11,12	mouse	(G)	13 wk 5 d/wk		500		1000 (3/10F died)	NTP 1986

Table 2-2 (continued)

Graph Key	Species	Route[a]	Exposure Frequency/ Duration	Effect	NOAEL[b]	LOAEL[c] (Effect) Less Serious (mg/kg/day)	LOAEL[c] (Effect) Serious	Reference
Systemic								
13	rat	(F)	90 d	Resp	311.8			AME Inc 1972a
				Cardio	311.8			
				Gastro	311.8			
				Hemato	311.8			
				Musc/Skel	311.8			
				Hepatic	311.8			
				Renal	311.8			
				Derm/Oc	311.8			
				Other	311.8[d]			
14	rat	(G)	13 wk 5 d/wk	Resp	1000			NTP 1986
				Cardio	1000			
				Gastro	1000			
				Hemato	1000			
				Hepatic	1000			
				Renal	1000			
				Derm/Oc	1000			
				Other	1000			
15	mouse	(G)	13 wk 5 d/wk	Resp	1000			NTP 1986
				Cardio	1000			
				Gastro	1000			
				Hemato	1000			
				Hepatic	1000			
				Renal	1000			
				Derm/Oc	1000			
				Other	1000			
16	dog	(C)	90 d	Resp	150			AME Inc 1972b
				Cardio	150			
				Gastro	150			
				Hemato	150			
				Musc/skel	150			
				Hepatic	150			
				Renal	150			
				Derm/Oc	150			
				Other	150			

Table 2-2 (continued)

Graph Key	Species	Route[a]	Exposure Frequency/ Duration	Effect	NOAEL[b]	LOAEL[c] (Effect) Less Serious (mg/kg/day)	LOAEL[c] (Effect) Serious	Reference
Neurological								
17	rat	(G)	13 wk 5 d/wk			1000[e] (lethargy)		NTP 1986
18	mouse	(G)	16 d 5 d/wk (12 doses 16 d)			1000[e] (stagger)		NTP 1986
CHRONIC EXPOSURE								
Death								
19,20	rat	(G)	103 wk 5 d/wk		250		500 (increased mortality)	NTP 1986
Systemic								
	rat	(G)	103 wk 5 d/wk	Resp	500			NTP 1986
				Cardio	500			
				Gastro	500			
				Hemato	500			
21				Renal		250 (nephropathy)		
				Derm/Oc	500			
22				Other	500			
	mouse	(G)	103 wk 5 d/wk	Resp	500			NTP 1986
				Cardio	500			
23				Gastro		250 (hyperkeratosis)		
				Hemato	500			
24				Hepatic		250[f] (necrosis)		
25				Renal		500 (inflammation)		
26				Other	500			

Table 2-2 (continued)

Graph Key	Species	Route[a]	Exposure Frequency/ Duration	Effect	NOAEL[b]	LOAEL[c] (Effect) Less Serious (mg/kg/day)	LOAEL[c] (Effect) Serious	Reference
Cancer								
27 28	rat	(G)	103 wk 5 d/wk				250 (CEL[g]-kidney tumors) 500 (CEL[g]-preputial gland tumors)	NTP 1986
29 30	mouse	(G)	103 wk 5 d/wk				250 (CEL[g]-lymphoma) 500 (CEL[g]-liver, integumentary system tumors)	NTP 1986

[a]G - Gavage, F - feed, C - capsule
[b]NOAEL - No Observed Adverse Effect Level
[c]LOAEL - Lowest Observed Adverse Effect Level
[d]Used to derive intermediate MRL: Uncertainty Factor of 100 (10 for intraspecies variability, 10 for interspecies variability) applied, resulting in a MRL of 3 mg/kg/day.
[e]Plotted under acute duration - see text.
[f]Used to derive chronic MRL: Uncertainty Factor of 1000 (10 for intraspecies variability, 10 for interspecies variability, 10 for use of a LOAEL) applied resulting in a MRL of 0.2 mg/kg/day.
[g]CEL - Cancer Effect Level

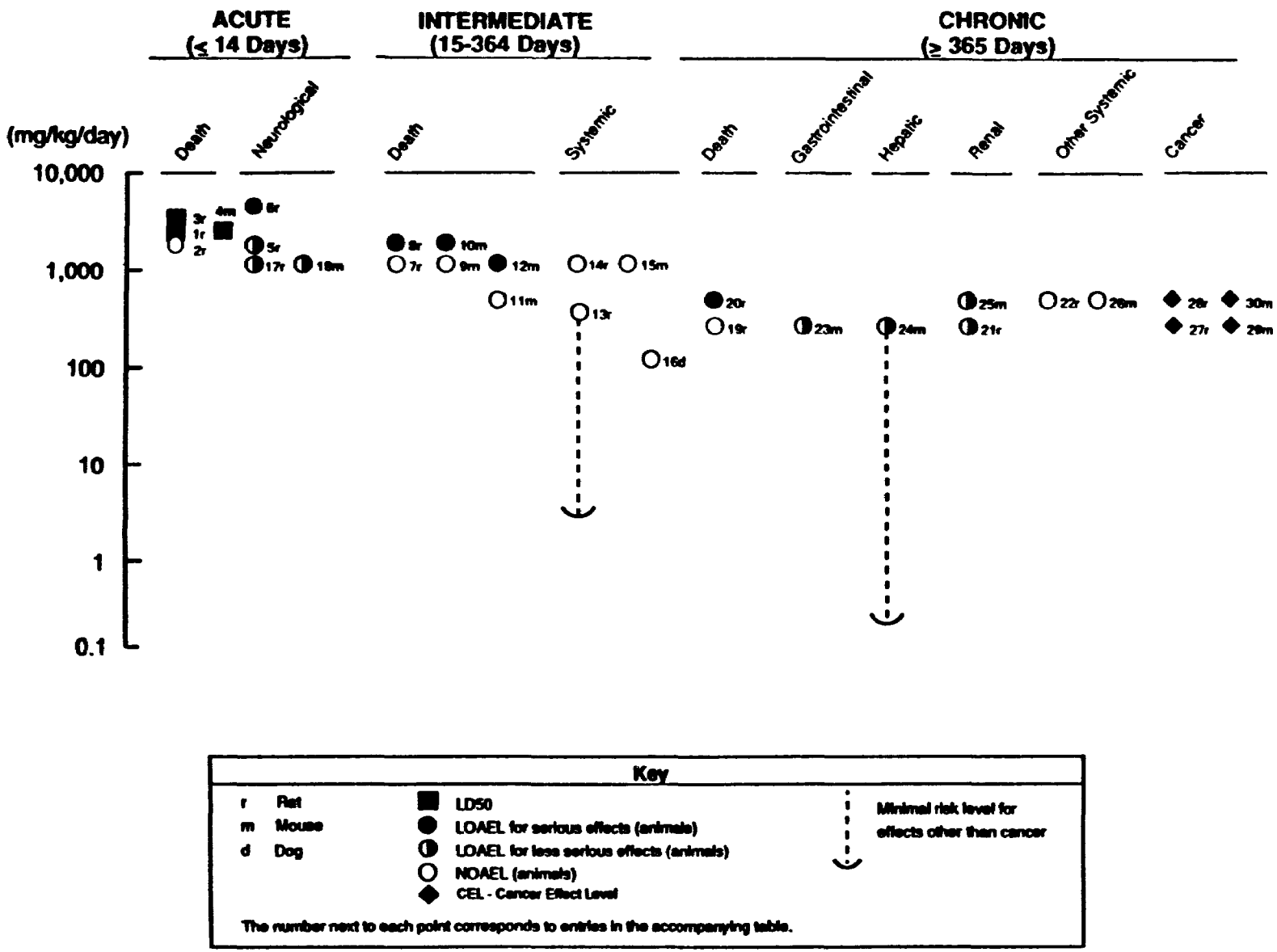


FIGURE 2-2. Levels of Significant Exposure to Isophorone - Oral

lethality in rats and mice. For the 13-week study, 1000 mg/kg/day is the LOAEL for lethality and 500 mg/kg/day is the NOAEL for lethality in mice (see Table 2-2 and Figure 2-2). Although the deaths were considered to be related to isophorone exposure, NTP (1986) did not comment on the cause of death. At 1000 mg/kg/day in the 13-week study, one female rat died during week 5, but NTP (1986) did not comment on whether this death was considered to be related to isophorone exposure.

In the chronic exposure experiment by NTP (1986), male rats treated with 500 mg/kg/day (LOAEL for lethality due to chronic oral exposure on Table 2-2 and Figure 2-2) showed increased mortality, while no increased mortality was observed at 250 mg/kg/day (NOAEL on Table 2-2 and Figure 2-2). NTP (1986) regarded the increased mortality in the male rats to be related to treatment with isophorone, but the cause was not attributed to lesions in any one particular organ system. The increased mortality occurred late in the study (after 96 weeks). No long-term studies of isophorone administered in food or drinking water demonstrating increased mortality were located. The dose levels of 1000 and 2000 mg/kg/day, which were administered to mice by gavage in corn oil for 16 days and 13 weeks (NTP 1986), respectively, were converted to equivalent concentrations of 8000 and 15,000 ppm in food for presentation in Table 1-4.

2.2.2.2 Systemic Effects

No reliable studies were located regarding the systemic effects in animals following acute oral exposure to isophorone.

Gastrointestinal Effects. In generally well-conducted, comprehensive 90-day studies, no treatment-related grossly or histologically observable lesions were found in the gastrointestinal tract of rats and mice dosed by gavage with isophorone (NTP 1986), rats exposed to isophorone in the diet (AME Inc 1972a), or dogs treated with isophorone in gelatine capsules (AME Inc 1972b). The studies by AME Inc (1972a,b) had several limitations, which include lack of reporting of chemical analysis of feed formulations and statistical methods in the rat study, and failure to examine all animals histologically in both studies. Despite the limitations, the results reported for gastrointestinal effects, as well as for other endpoints, are probably valid because the doses are lower than the NOAELs for the same endpoints in the NTP (1986) 90-day (13-week) study. The highest doses administered in these studies were 311.8 mg/kg/day in the diet in rats (AME Inc 1972a), 1000 mg/kg/day by gavage in rats and mice (NTP 1986), and 150 mg/kg/day in dogs (AME Inc 1972b), which are indicated as NOAELs for systemic toxicity due to intermediate oral exposure in Table 2-2 and Figure 2-2.

In the chronic gavage study by NTP (1986), hyperkeratosis of the forestomach was observed in isophorone-treated mice at both doses (Table 2-2 and Figure 2-2), but not in rats. The lowest dose of 250 mg/kg/day is indicated as a LOAEL for less serious gastrointestinal effects due to

chronic oral exposure to isophorone. No long-term studies of isophorone administered in food or drinking water demonstrating gastrointestinal effects were located. The dose level of 250 mg/kg/day, which was administered by gavage in corn oil (NTP 1986), was converted to an equivalent concentration of 1900 ppm in food for presentation in Table 1-4.

Hepatic Effects. No significant differences between pre-exposure and post-exposure levels of serum electrolytes, blood glucose and sulfhydride radicals, SGOT, SGPT, serum creatine phosphokinase, or serum lactic dehydrogenase were found in rabbits treated by gavage with isophorone at a dose of 1000 mg/kg/day, 2 days/week for 2 weeks (Dutertre-Catella 1976). No other indices of liver toxicity were examined; therefore, the dose of 1000 mg/kg/day cannot be considered a NOAEL for liver effects. In the 90-day studies conducted by NTP (1986) and AME Inc (1972a,b), no treatment-related grossly or histologically observable lesions were found in the livers of rats and mice dosed by gavage with isophorone (NTP 1986), rats treated with isophorone in the diet (AME Inc 1972a), or dogs treated with isophorone in gelatine capsules (AME Inc 1972b). These studies were comprehensive and generally well-conducted. The highest doses administered in these studies were 311.8 mg/kg/day in the diet in rats (AME Inc 1972a), 1000 mg/kg/day by gavage in rats and mice (NTP 1986), and 150 mg/kg/day in dogs (AME Inc 1972b), which are indicated as NOAELs for systemic effects due to intermediate oral exposure in Table 2-2 and Figure 2-2.

No treatment-related gross or histopathological lesions in the liver were observed in rats in the chronic experiment by NTP (1986), but dosed male mice had increased coagulative necrosis and hepatocytomegaly, along with increased incidences of hepatocellular adenomas and carcinomas (see Section 2.2.2.8 on carcinogenicity). Female mice, however, did not have treatment-related lesions in the liver. The highest dose (500 mg/kg/day) is indicated as a NOAEL for liver effects in rats, while the low dose (250 mg/kg/day) is indicated as a LOAEL for non-neoplastic liver lesions in mice due to chronic oral exposure to isophorone (see Table 2-2 and Figure 2-2). No long-term studies of isophorone administered in food or drinking water demonstrating hepatic effects were located. The dose level of 250 mg/kg/day, which was administered by gavage in corn oil (NTP 1986), was converted to an equivalent concentration of 1900 ppm in food for presentation in Table 1-4.

Renal Effects. Gross and histological examination of the kidneys of rats and mice treated with isophorone by gavage (NTP 1986), rats fed diets containing isophorone (AME Inc 1972a), or dogs treated with isophorone in gelatine capsules (AME Inc 1972b) for 90 days revealed no treatment-related lesions. In the NTP (1986) 90-day studies, recuts and special stains of kidney tissues were performed to confirm the lack of response on the kidney. Thus, the highest doses administered in these studies (311.8 mg/kg/day in the diet in rats, 1000 mg/kg/day by gavage in rats and mice, and 150 mg/kg/day in dogs (AME Inc 1972b) are NOAELs for systemic effects due to intermediate oral exposure (see Table 2-2 and Figure 2-2).

The kidney is a target organ for chronic oral exposure to isophorone. In the NTP (1986) study, dosed male mice, but not female mice, had increased incidences of chronic focal inflammation of the kidney, but no other lesions. The 500 mg/kg/day dose is indicated as a LOAEL for less serious renal effects in mice due to chronic oral exposure in Table 2-2 and Figure 2-2. Dosed male rats had increased incidences of tubular cell hyperplasia (possibly pre-neoplastic), epithelial cell hyperplasia of the renal pelvis, and tubular mineralization at both doses. The incidence of tubular mineralization was higher in low dose males than in high dose males, and was coincident with chronic nephropathy, the incidence of which was also higher at the low dose. For this reason, NTP (1986) stated that the nephropathy was probably not the cause of the increased mortality in the high dose males. Male rats also had increased incidences of tubular cell adenomas and carcinomas (see Section 2.2.2.8 on carcinogenicity). As discussed in Section 2.3 (Relevance to Public Health), the tubular cell lesions may be unique to male rats. Dosed female rats had increased incidences of nephropathy, which may have been related to isophorone exposure. The dose of 250 mg/kg/day is indicated as a LOAEL for less serious effects on the kidney in rats for chronic oral exposure to isophorone in Table 2-2 and Figure 2-2. No long-term studies of isophorone administered in food or drinking water demonstrating renal effects were located. The dose level of 250 mg/kg/day, which was administered by gavage in corn oil (NTP 1986), was converted to an equivalent concentration of 5000 ppm in food for presentation in Table 1-4.

Other Systemic Effects. Mean body weight gain was decreased in rats treated by gavage with isophorone at 1000 mg/kg/day, but not at 500 mg/kg/day in a 16-day experiment by NTP (1986). The mice in the 16-day study did not have decreased growth. Body weight changes were not consistent or dose-related in the rats or mice treated with up to 1000 mg/kg/day in the 13-week experiment or up to 500 mg/kg/day in the 103-week experiment (NTP 1986). Male rats treated with 233.8 mg/kg/day had transient decreases in body weight gain during the 90-day feeding study by AME Inc (1972a), but body weights were not significantly different from controls at the end of the study. As 1000 mg/kg/day was a NOAEL for body weight changes in rats and mice in 13-week experiments, the decreased mean body weight at the same dose in the 16-day study cannot be considered an adverse effect. Therefore, 1000 mg/kg/day is a NOAEL for body weight changes in rats and mice for intermediate duration exposure.

In the well-conducted, comprehensive 90-day studies, no treatment-related grossly or histologically observable lesions were found in the lungs, hearts, hematopoietic tissues, or in the skin or eyes of rats and mice dosed by gavage with isophorone (NTP 1986), rats treated with isophorone in the diet (AME Inc 1972a), or dogs treated with isophorone in gelatine capsules (AME Inc 1972b). Furthermore, no changes in hematological indices and no histopathological lesions in the skeletal muscle were found in rats or dogs in the studies by AME Inc (1972a,b).

highest doses administered in these studies were 311.8 mg/kg/day in the diet in rats (AME Inc 1972a), 1000 mg/kg/day by gavage in rats and mice (NTP 1986), and 150 mg/kg/day in dogs (AME Inc 1972b), which are indicated as NOAELs for systemic effects due to intermediate oral exposure in Table 2-2 and Figure 2-2.

A *minimal risk level (MRL) for intermediate oral exposure* can be derived from the NOAELs for systemic endpoints. The highest NOAELs for systemic effects of intermediate oral exposure were the 1000 mg/kg/day doses in rats and mice in the 13-week (NTP 1986) study. Increased mortality was observed in mice at 1000 mg/kg/day, however, precluding the use of this dose. Based on the dose of 311.8 mg/kg/day in rats (AME Inc 1972a), an intermediate duration oral MRL of 3 mg/kg/day was calculated, as described in the footnote in Table 2-2. The MRL for intermediate exposure can be compared to existing State and Federal criteria levels (see Chapter 7) or to amounts of the chemical encountered in environmental or occupational situations (see Chapter 5).

Other than the gastrointestinal, hepatic, and renal lesions described above, no treatment-related gross or histopathological lesions were observed in the lungs, heart, hematopoietic organs, skin, or other organs and tissues of rats and mice in the chronic experiment by NTP (1986). There was a dose-related increased incidence of fatty metamorphosis of the adrenal cortex in the male rats, but NTP (1986) stated that the biological significance of this observation is not known. The highest dose (500 mg/kg/day) is indicated as a NOAEL for systemic effects other than gastrointestinal, hepatic, and renal toxicity due to chronic oral exposure to isophorone (Table 2-2 and Figure 2-2). As discussed above under these endpoints, the LOAEL for gastrointestinal, hepatic, and renal effects is 250 mg/kg/day, (as the dose was given 5 days/week, it is equivalent to 179 mg/kg/day). A MRL for chronic oral exposure can be derived from the LOAELs for systemic effects. Based on the dose of 179 mg/kg/day, a chronic oral MRL of 0.2 mg/kg/day was calculated as described in the footnote to Table 2-2. The MRL has been converted to an equivalent concentration in food (7 ppm) for presentation in Table 1-3.

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in animals following acute oral exposure to isophorone.

Histological examination of organs and tissues of the immune system did not reveal any effects in rats or mice treated by gavage with isophorone for 13 or 103 weeks (NTP 1986), in rats treated with isophorone in the diet for 13 weeks (AME Inc 1972a), or in dogs treated with isophorone in gelatine capsules for 13 weeks (AME Inc 1972b). In none of these studies, however, were specific tests of immune function performed. Such tests of immune function are more likely to detect immunological effects than are

histological examinations. Therefore, the doses used in these studies cannot be considered NOAELs for effects on the immune system.

2.2.2.4 Neurological Effects

Neurological effects of isophorone have been observed in animals after oral dosing. In an acute study, rats treated by gavage with isophorone at 5000 mg/kg displayed depression, ptosis, absence of righting reflex, and prostration (LOAEL for serious effects due to acute oral exposure on Table 2-2 and Figure 2-2); 4/5 died within 2 days after dosing (Hazleton Labs 1964). At 1450 mg/kg, depression was observed but the rats recovered withi 2 days (LOAEL for less serious effects for acute oral exposure in Table 2-2 and Figure 2-2). No signs of neurotoxicity occurred at 417 mg/kg. In the 16-day NTP (1986) study, mice treated by gavage at 1000 mg/kg/day, but not at 500 mg/kg/day, staggered after dosing, indicating an acute response to the high dose. Similarly, in the 13-week NTP (1986) study, rats given 1000 mg/kg/day, but not 500 mg/kg/day, were sluggish and lethargic after dosing, also indicating an acute response to the high dose. Therefore, 1000 mg/kg is the acute LOAEL for less serious neurological effects (Table 2-2 and Figure 2-2). Although the doses of 417 mg/kg and 500 mg/kg did not result in overt signs of neurotoxicity, more sensitive tests for neurotoxicity (e.g., operant performance, motor activity, electrophysiology), which may have revealed neurobehavioral effects at these doses, were not performed. Therefore, these doses should not be considered NOAELs for neurotoxicity fo: oral exposure. No short-term studies of isophorone administered in food or drinking water were located. The dose level of 1000 mg/kg in mice, which was administered by gavage in corn oil (NTP 1986), was converted to an equivalent concentration of 8000 ppm in food for presentation in Table 1-4.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals following oral exposure to isophorone.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in animals following acute oral exposure to isophorone.

Histological examination of reproductive organs did not reveal any effects in rats or mice treated by gavage with isophorone for 13 or 103 weeks (NTP 1986), in rats treated with isophorone in the diet for 13 weeks (AME Inc 1972a), or in dogs treated with isophorone in gelatine capsules for 13 weeks (AME Inc 1972b). In none of these studies, however, were specific tests of reproductive function performed, which would be necessary to rule out an effect. Therefore, the doses used in these studies cannot be considered NOAELs for effects on reproduction.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following oral exposure to isophorone.

2.2.2.8 Cancer

In the chronic gavage study, NTP (1986) concluded that there is "some evidence of carcinogenicity" in male rats due to an increased incidence of relatively rare renal tubular cell adenomas and adenocarcinomas at 250 and 500 mg/kg/day and rare preputial gland carcinomas at 500 mg/kg/day. According to the strict criteria of NTP, "some evidence" in this case means that the study showed a slight increase in uncommon malignant or benign neoplasms. The 250 and 500 mg/kg/day doses are indicated in Table 2-2 and Figure 2-2 as effect levels for carcinogenicity (Cancer Effect Levels, CELs) in rats due to oral exposure to isophorone. Based on the combined incidences of renal tubular cell tumors and preputial gland tumors, EPA (1986, 1987b) proposed an oral q_1^* of 4.1×10^{-3} $(mg/kg/day)^{-1}$ for isophorone, but this analysis is under review by the EPA.

In the NTP (1986) study, male mice had marginally increased incidences of hepatocellular tumors and mesenchymal tumors of the integumentary system at 500 mg/kg/day and of malignant lymphomas at 250 mg/kg/day. NTP (1986) considered this evidence to be equivocal because the study showed marginal increases in neoplasms related to isophorone exposure. The doses of 250 and 500 mg/kg/day are indicated in Table 2-2 and Figure 2-2 as CELs for carcinogenicity in mice. There was no evidence of carcinogenicity in female rats or mice.

2.2.3 Dermal/Ocular Exposure

No studies were located regarding health effects in humans following dermal or ocular exposure to isophorone.

2.2.3.1 Death

Hazleton Labs (1964) reported that the dermal LD_{50} of isophorone in rabbits was greater than 3160 mg/kg, the highest dose tested. In this study, the area of application was occluded for 24 hours. Union Carbide (1968), however, reported 1.5 mL/kg (1384 mg/kg) as the dermal LD_{50} in rabbits, but no details of the determination were provided. Therefore, it is not possible to reconcile these contradictory reports. Dutertre-Catella (1976) estimated a dermal LD_{50} of 1200 mg/kg in rabbits. The LD_{50} was difficult to determine with precision because some rabbits died within 6 hours of application and the method requires that the chemical remain on the skin for 24 hours. The rabbits that did not die within 6 hours recovered and were not harmed by doses up to 4000 mg/kg. The dermal LD_{50} is indicated on Table 2-3. When 0.1 or 0.2 mL isophorone was applied to the shaved skin of

Table 2-3. Levels of Significant Exposure to Isophorone - Dermal[a]

	Species	Exposure Frequency/ Duration	Effect	NOAEL[c]	LOAEL[b] (Effect) Less Serious	LOAEL[b] (Effect) Serious	Reference
ACUTE EXPOSURE							
Death							
	rabbit	once				1200 mg/kg (LD_{50})	Dutertre-Catella 1976
Systemic							
	guinea pig	once 24 hr	Dermal		dose not specified (irritation)		Eastman Kodak 1967
	rabbit	once	Dermal		0.5 ml (irritation)		Truhaut et al. 1972
	rabbit	once	Ocular			0.02 ml (eye necrosis)	Carpenter and Smyth 1946
	rabbit	30 sec	Ocular			0.1 ml (corneal opacity)	Hazleton Labs 1964
	rabbit	once 24 hr	Dermal	50 mg/kg	200 mg/kg (desquamation)		Hazleton Labs 1964
	rabbit	once 1 or 4 h	Dermal		0.5 ml (irritation)		Potokar et al. 1985
	rabbit	once	Ocular			0.1 ml (eye injury)	Truhaut et al. 1972
Neurological							
	rabbit	once 24 hr		794 mg/kg		3160 mg/kg (CNS depression)	Hazleton Labs 1964

Table 2-3 (continued)

Species	Exposure Frequency/ Duration	Effect	NOAEL[c]	LOAEL[b] (Effect) Less Serious	LOAEL[b] (Effect) Serious	Reference
INTERMEDIATE EXPOSURE						
Death						
rat	8 wk 7 d/wk				0.1 ml (death of 20% males)	Dutertre-Catella 1976
Systemic						
rat	8 wk 7 d/wk			0.1 ml (erythema and scar tissue)		Dutertre-Catella 1976

[a]These levels are not displayed graphically because none of the studies used doses expressed in units of $mg/cm^2/day$

[b]LOAEL - Lowest Observed Adverse Effect Level

[c]NOAEL - No Observed Adverse Effect Level

rats for 8 weeks, 20% of the males but none of the females died (Dutertre-Catella 1976) (Table 2-3). No studies were located regarding death of animals following chronic duration exposure to isophorone.

2.2.3.2 Systemic Effects

Dermal/Ocular Effects. Skin irritation was observed in rabbits and guinea pigs following dermal application of isophorone (Eastman Kodak 1967; Hazleton Labs 1964; Potokar et al. 1985; Truhaut et al. 1972). In these studies, undiluted isophorone generally in a volume of 0.5 ml (Table 2-3) was applied to the clipped skin of the animals and held under an occlusive covering. Hazleton Labs (1964) reported doses in units of mg/kg and found that ≥200 mg/kg (LOAEL for less serious effects) resulted in desquamation and erythema, while 50 mg/kg (NOAEL) was without effect. Application of 0.1 or 0.2 mL isophorone to the shaved skin of rats for 8 weeks resulted in erythema and scar tissue formation (Dutertre-Catella 1976). These effects disappeared rapidly after exposure ceased. These doses are indicated in Table 2-3.

Isophorone is also irritating to the eyes of rabbits. Application of 0.02-0.1 ml of undiluted isophorone directly to the eye caused severe injury, corneal opacity, and necrosis (Carpenter and Smyth 1946; Hazleton Labs 1964; Truhaut et al. 1972) (see Table 2-3). Hazleton Labs (1964) found that the corneal damage was no longer present 14 days after exposure. No studies were located regarding dermal/ocular effects in animals following intermediate or chronic duration exposure to isophorone.

Other Systemic Effects. In rabbits exposed dermally to isophorone at doses up to 3160 mg/kg, no systemic pathological effects were found by gross necropsy (Hazleton Labs 1964), but histological examinations were not performed. In this study, the site of application was occluded for 24 hours to prevent evaporation of isophorone from the skin. No significant differences between pre-exposure and post-exposure levels of serum electrolytes, blood glucose and sulfhydride radicals, SGOT, SGPT, serum creatine phosphokinase, or serum lactic dehydrogenase were found in rabbits treated dermally with 20 mL isophorone (Dutertre-Catella 1976). No other indices of liver toxicity were examined; therefore, the 20 mL dose cannot be considered a NOAEL for liver effects.

2.2.3.3 Immunological Effects

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

2.2.3.4 Neurological Effects

In the study by Hazleton Labs (1964), 1/4 rabbits exposed dermally to 3160 mg/kg under an occlusive bandage for 24 hours displayed marked depression, labored respiration, sprawling, and depressed reflexes (see

Table 2-3). The other three rabbits at this dosage and at ≤794 mg/kg did not display any signs of toxicity.

No studies were located regarding the following effects in humans or animals following dermal or ocular exposure to isophorone:

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

2.3 RELEVANCE TO PUBLIC HEALTH

Death. No information was located regarding death of humans following inhalation, oral, or dermal exposure to isophorone. Concentrations and doses causing death in animals have been reported for acute and intermediate duration inhalation exposures, for acute, intermediate duration, and chronic oral exposures, and for acute and intermediate duration dermal exposure. The acute lethality of isophorone in animals may be due to its effects on the central nervous system. Hazleton Labs (1964) found that rats exposed by inhalation to the LC_{50} were comatose, and rats treated orally with lethal doses displayed depression, absence of righting reflex, and prostration. In the gavage NTP (1986) studies, rats and mice displayed lethargy and staggering after dosing with 1000 mg/kg. The highest dose in the 16-day study (2000 mg/kg/day) was fatal to all the mice and 5/10 of the rats. NTP (1986) did not comment on the cause of death. In the chronic study, high-dose (500 mg/kg/day) male rats had increased mortality (NTP 1986). The increased mortality, which occurred late in the study (after 96 weeks), was considered to be related to isophorone exposure, but NTP (1986) could not relate the cause with effects in any specific organ system. The concentrations or doses of isophorone that would be required to result in the death of humans are not known. As mild neurological effects have been observed in humans exposed to relatively low levels of isophorone, it is likely that if humans were to be exposed to levels high enough to result in death, the cause may be related to more severe CNS effects.

Systemic Effects. The only known effects of isophorone exposure in humans are eye, nose, and throat irritation, and fatigue and malaise. Studies were conducted in humans to determine the thresholds for eye, nose, and throat irritation (25-35 ppm) (Hazleton Labs 1965b; Silverman et al. 1946). The thresholds agree reasonably well with exposure concentrations (≈25 ppm) associated with eye, nose, and skin irritation in occupational settings (Kominsky 1981; Lee and Frederick 1981). The thresholds for irritation are near the OSHA (1989) Permissible Exposure Limit of 25 ppm, and higher than the ACGIH (1988) Ceiling Limit of 5 ppm, which is based on worker complaints of fatigue and malaise (ACGIH 1986).

2. HEALTH EFFECTS

Systemic effects of isophorone observed in animals include pulmonary congestion and hemorrhage, hyperkeratosis of the forestomach, irritation to the skin, eye, and mucous membranes, hematological effects, liver damage, and kidney damage.

The hemorrhaging observed in rats and rabbits (Dutertre-Catella 1976) and the pulmonary congestion observed in rats and mice following acute inhalation exposure to isophorone (Hazleton Labs 1964) is probably related to irritation of mucous membranes. DeCeaurriz et al. (1981a) assessed the sensory irritation of isophorone in mice by measuring the decrease in the respiratory rates, also indicating that isophorone is irritating to the respiratory system. Ocular and nasal irritation also occurred in rats exposed to isophorone in air at 500 ppm for up to 6 months and in rats and rabbits exposed to 250 ppm for 18 months (Dutertre-Catella 1976). Since isophorone is known to be irritating to mucous membranes of humans, inhalation exposure probably could result in pulmonary congestion in humans. The highest inhalation exposures occur in occupational settings, however, where respiratory irritation has been reported in humans exposed to isophorone and other solvents.

Chronic exposure of mice by gavage to isophorone at 250 mg/kg/day resulted in hyperkeratosis of the forestomach (NTP 1986), an effect that may also be related to the irritating effect on mucous membranes. Although there is no tissue in man that is precisely analogous to the mouse forestomach and the effects of oral exposure of humans to isophorone are not known, ingestion of isophorone could result in gastrointestinal irritation. The minimum concentration of isophorone in water or food necessary to produce the irritation cannot be determined from the available data in animals.

Dermal exposure of rats, rabbits, and guinea pigs results in skin irritation (Dutertre-Catella 1976; Eastman Kodak 1967; Hazleton Labs 1964; Potokar et al. 1985; Truhaut et al 1972). In these studies, liquid isophorone was applied to the skin and the area of application was occluded for 24 hours to prevent evaporation, or to the shaved skin for 8 weeks. While it is unlikely that a human would be exposed in such a manner, screen printers are exposed dermally to both the vapor and the liquid forms of isophorone, which could result in irritation of unprotected skin.

Application of undiluted isophorone to the eyes of rabbits results in severe eye injury (Carpenter and Smyth 1946; Hazleton Labs 1964; Truhaut et al. 1972), which appears to be reversible with time (Hazleton Labs 1964). Isophorone is known to be irritating to the eyes of humans exposed to the vapors (Hazleton Labs 1968; Silverman et al. 1946); it is reasonable to conclude that liquid isophorone splashed directly into the eyes of humans could cause severe eye injury.

When post-exposure values were compared with pre-exposure values, slight changes in the percentage of white blood cells and slightly increased hemoglobin content were observed in rats exposed to isophorone by inhalation (Hazleton Labs 1964), but similar changes also occurred in controls. Therefore, toxicological significance of this finding is minimal and the relevance to humans is not known.

Reported effects on the liver include decreased liver weight in rats exposed subchronically by inhalation (Hazleton Labs 1968), cytoplasmic microvacuolization in rats exposed chronically by inhalation (Dutertre-Catella 1976), and increased incidence of coagulative necrosis and hepatocytomegaly in male mice exposed chronically by gavage at 250 and 500 mg/kg/day (NTP 1986). The decreased liver weight in rats exposed by inhalation is of questionable toxicological significance because histological examination of a limited number of rats in the study did not reveal treatment-related liver lesions. The toxicological significance of the microvacuolization observed in liver cells of rats and rabbits is also unknown. The liver lesions observed in male mice in the oral study were not observed in female mice, but the reason for the sex difference is not known. The mechanism by which isophorone produces liver lesions in male mice is not known, but liver lesions are common in aged mice; isophorone may enhance an age-related process. It is not known whether isophorone causes liver effects or enhances age-related processes in humans.

Subchronic inhalation studies of isophorone (Smyth and Seaton 1940; Smyth et al. 1942) reported severe kidney damage in rats and guinea pigs, but these studies have been criticized for using impure isophorone and for overestimating the exposure concentration (Rowe and Wolf 1963). Because of these reports, however, NTP (1986) examined the kidneys twice and used special staining techniques to confirm the lack of histopathological lesions and protein droplets in the kidneys of rats and mice exposed subchronically to isophorone by gavage. Although the NTP (1986) study did not detect protein droplet formation in the kidneys of rats or mice treated with isophorone (Bucher 1988), protein droplets were found in the kidneys of male rats exposed by inhalation to dihydroisophorone (Hazleton Labs 1968), a metabolite of isophorone. Furthermore, Strasser (1988) found that isophorone and its metabolites, dihydroisophorone and isophorol, induced significant protein droplet formation in the kidneys of male rats treated acutely by gavage. It was not clear if the response was dose-related.

Isolation and analysis of $\alpha_{2\mu}$-globulin from the kidney cytosol of rats treated with isophorone or dihydroisophorone positively identified isophorone or dihydroisophorone, respectively, in the $\alpha_{2\mu}$-globulin samples. Following treatment with isophorol, isophorone was found in the $\alpha_{2\mu}$-globulin samples, indicating that isophorol was metabolized to isophorone. The results of Strasser (1988) are preliminary and require confirmation, but the data suggest that isophorone and its metabolites bind to $\alpha_{2\mu}$-globulin and induce protein droplet nephropathy in male rats.

$\alpha_{2\mu}$-Globulin is a low molecular weight protein synthesized in large quantities in the male rat liver, secreted into the blood under the influence of testosterone (Alden 1986), and filtered through the glomerulus. The $\alpha_{2\mu}$-globulin is reabsorbed by the tubule cells and sequestered into lysosomes, where it is catabolized into amino acids and peptides. In the normal rat kidney, the rate of catabolism of $\alpha_{2\mu}$-globulin is relatively slow compared with that of other proteins (Swenberg et al. 1989). In the male F344 rat, protein droplet nephropathy is characterized by accumulation of $\alpha_{2\mu}$-globulin in lysosomes, degeneration and necrosis of tubular cells, formation of granular casts, and regeneration (proliferation) of the tubular epithelium (Swenberg et al. 1989). Chemicals that are known to induce protein droplet nephropathy bind to $\alpha_{2\mu}$-globulin, yielding a complex that may be more resistant to the proteolytic enzymes in the lysosomes, which leads to the accumulation of the complex in the tubule cells.

$\alpha_{2\mu}$-Globulin has not been found in immature male rats, female rats, or humans (Alden 1986). In adult male rats, the protein may function as a pheromone carrier (Alden 1986). If isophorone induces nephropathy by the suggested mechanism, the absence of $\alpha_{2\mu}$-globulin in humans raises the question of the relevance to humans of the isophorone-induced kidney lesions in male rats. $\alpha_{2\mu}$-Globulin is related to other low molecular weight transport proteins that have been detected in humans (Swenberg et al. 1989), but it is not known whether chemicals that are nephrotoxic to the rat will bind to the human proteins or produce similar effects in humans.

In the chronic gavage study by NTP (1986), dosed male rats had increased incidences of renal tubular cell hyperplasia, epithelial cell hyperplasia of the renal pelvis, and tubular mineralization. The male rats also had increased incidences of renal tubular cell tumors. The hyperplasia of the tubular cells, therefore, may represent a preneoplastic response (see discussion of cancer below). These proliferative kidney lesions were not observed in male or female mice or in female rats. The mechanism for the induction of proliferative kidney lesions may also be related to $\alpha_{2\mu}$-globulin-induced nephropathy (see discussion of cancer below), again raising the question of the relevance of the proliferative kidney lesions in male rats to humans. This issue is presently the subject of scientific investigation.

Female rats had increased incidences of age-related nephropathy (NTP 1986). The tubular mineralization in the male rats was coincident with age-related nephropathies, which were more severe in the low-dose males. It is possible, therefore, that isophorone treatment enhanced the age-related nephropathies commonly seen in rats, but it is not known if isophorone could enhance age-related processes in humans.

Neurological Effects. Humans occupationally exposed to isophorone at levels as low as 5-8 ppm have complained of fatigue and malaise (Ware 1973). When workroom levels were lowered to 1-4 ppm, complaints ceased. Neurological effects of oral or dermal exposure of humans to isophorone are

not known. Acute exposure of animals to high inhalation concentrations and oral and dermal doses affects the central nervous system as evidenced by such effects as narcosis, staggering, depression, ataxia, lethargy, and prostration and coma. No histologically detectable lesions have been found in the brain, sciatic nerve, or spinal cord of animals exposed to isophorone by any route for any duration. Although not precisely known, the mechanism by which isophorone induces its neurological effects may involve interference with neuronal impulse transmissions via physical interaction of isophorone with nerve membrane components, as is seen with many organic solvents. The effects in animals at high exposures and the malaise and fatigue in humans at relatively low workroom concentrations of isophorone predict that exposure of humans to high air concentrations or high oral doses could result in severe central nervous system depression.

Developmental Effects. Isophorone has been tested by inhalation for developmental effects in rats and mice. Evidence for intrauterine growth retardation was seen at an exposure concentration of 115 ppm (Bio/dynamics 1984a,b). At 150 ppm, exencephaly was seen in several fetuses. While the incidence of this malformation was not statistically significant, it was seen in both species and only in treated animals. Dose-related maternal toxicity was evident in all treatment groups. Isophorone has not been tested for developmental effects by the oral or dermal route. No studies were located demonstrating that isophorone crosses the placenta in animals or in humans, but there is no reason to assume that it does not do so. It is not known whether isophorone could cause developmental effects in humans.

Genotoxic Effects. No studies were located regarding the genotoxicity of isophorone in humans or animals by the inhalation, oral, or dermal routes. Isophorone has been tested for genotoxic effects in vitro and in mice treated intraperitoneally (Table 2-4). Isophorone was negative for reverse mutations with and without metabolic activation with S9 prepared from rat or hamster livers (NTP 1986). CMA (1984) reported that isophorone was negative both with and without metabolic activation in mouse lymphoma cells, while NTP (1986) found a weakly positive effect without activation in the same cell system. The concentrations of isophorone used by NTP (1986) were at least 60 times higher than those used by CMA (1984). Negative results were found for unscheduled DNA synthesis in rat hepatocytes, for chromosome aberrations in Chinese hamster ovary cells, and in the micronucleus test in mice (CMA 1984; NTP 1986). NTP (1986) found a positive response for sister chromatid exchange in Chinese hamster ovary cells in the absence, but not in the presence, of a metabolic activating system.

In assessing the potential for a chemical to produce heritable mutations in humans, it is necessary to examine the weight of evidence obtained from in vitro tests for mutations in microorganisms and cultured mammalian cells, from in vivo tests of mutations in animals, and from in vitro and in vivo tests for chromosome aberrations in mammalian cells. The strongest evidence would come from the demonstration that a chemical causes mutations or chromosome aberrations in human cells. As no studies were

TABLE 2-4. Genotoxicity of Isophorone In Vitro and In Vivo

End Point	Species (test system)	Result: Without activation	Result: With activation	References
Reverse mutation	*Salmonella typhimurium*	-	-	NTP 1986
Forward mutation	L5178Y/TK+/- mouse lymphoma cell	+	NT[a]	NTP 1986
		-	-	CMA 1984; McKee et al. 1987
UDS[b]	Rat primary hepatocyte	-	NA[c]	CMA 1984; McKee et al. 1987
SCE[d]	Chinese hamster ovary cells	+	-	NTP 1986
Chromosome aberrations	Chinese hamster ovary cells	-	-	NTP 1986
Micronucleus test	Mouse erythrocytes (mice treated i.p.)	-	NA[c]	CMA 1984; McKee et al. 1987

[a]Not tested.
[b]Unscheduled DNA synthesis.
[c]Not applicable.
[d]Sister chromatid exchange.

located that tested isophorone in cultured human cells or examined the cells of people with known exposure, this evidence is lacking. Of the five experiments that tested whether isophorone caused mutations or chromosome aberration in cultured mammalian cells, only two were positive: a weak mutagenic response in mouse lymphoma cells and a positive test for sister chromatid exchange in Chinese hamster ovary cells in the absence, but not in the presence, of metabolic activation were obtained by NTP (1986). Isophorone was not mutagenic in the Salmonella/microsome assay (NTP 1986). The only in vivo test was the micronucleus test in mice, which was negative (CMA 1984). Therefore, isophorone may be weakly genotoxic in mammalian cells, but the evidence is insufficient to predict that isophorone poses a genotoxic threat to humans.

Cancer. Increased incidences of relatively rare renal tubular cell adenomas and carcinomas were observed in male rats, but the increases were not statistically significant by the Fisher Exact test or the Cochran-Armitage test (NTP 1986). When adjusted for mortality, however, the increased incidences were significantly different from control in the high-dose males when analyzed by the Lifetable test and significant for dose-related trend by the Lifetable and the Incidental Tumor tests. As the kidney tumors were not fatal, the appropriateness of Lifetable test for the analysis of these tumors is questionable. The overall unadjusted incidences were significantly different from the historical control incidence by the Fisher Exact test. The kidney tumors were not observed in female rats or in male or female mice.

Isophorone is one of several diverse chemicals that have been found to induce kidney tubular cell tumors in male rats, but not in female rats, male or female mice, hamsters, guinea pigs, dogs, and nonhuman primates (Alden 1986; Swenberg et al. 1989). These chemicals include 1,4-dichlorobenzene, dimethymethylphosphonate, JP-5 jet fuel; d-limonene, pentachloroethane, tetrachloroethylene, and unleaded gasoline, which have also been found to cause protein droplet nephropathy in male rats. As discussed above for systemic renal effects, binding of these chemicals to $\alpha_{2\mu}$-globulin, a protein that appears to be unique to male rats, is believed to be involved in the protein droplet nephropathy. Based on tumor initiation-promotion studies of trimethylpentane, an $\alpha_{2\mu}$-globulin binding component of unleaded gasoline, and the body of data on $\alpha_{2\mu}$-globulin-induced protein droplet nephropathy, the following mechanism has been proposed for the formation of tumors in the male rat kidney (Swenberg et al. 1988). Accumulation of the chemical-$\alpha_{2\mu}$-globulin complex causes lysosomal protein overload and necrosis of the cells, with subsequent cellular regeneration that continues as long as the rat is exposed to the chemical and produces $\alpha_{2\mu}$-globulin. The increased cellular proliferation may promote tumorigenesis by increasing the number of cells in the kidney that have undergone spontaneous initiation. Given the findings of Strasser (1988) that isophorone was associated with $\alpha_{2\mu}$-globulin and induced protein droplet formation in the kidneys of male rats and that cell proliferation may be involved in the mechanism of male rat kidney tumorigenesis, the finding in the NTP (1986)

study of increased incidences of tubular epithelial hyperplasia in addition to the increased incidences of tubular cell tumors is consistent with the mechanism proposed by Swenberg et al. (1989).

As discussed above, $\alpha_{2\mu}$-globulin appears to be unique to male rats. If isophorone induces kidney tumors solely by the suggested mechanism, the absence of $\alpha_{2\mu}$-globulin in humans raises the question of the relevance to humans of the isophorone-induced kidney tumors in male rats. Although $\alpha_{2\mu}$-globulin is related to other low molecular weight transport proteins that have been detected in humans (Swenberg et al. 1989), it is not known whether chemicals that produce kidney tumors in male rats bind to the human proteins or produce similar effects in humans. This issue is currently being reviewed by the EPA.

Male rats treated with isophorone in the NTP (1986) study also had preputial gland carcinomas, an extremely rare finding. Analogous tissues in humans are modified sebaceous glands in the prepuce (foreskin of the penis), but it is not known whether isophorone could cause tumors in these glands or other glandular tissues in humans.

In male mice, significant dose-related trends by the Cochran-Armitage test were found for hepatocellular adenoma and carcinoma (combined) and for fibromas, sarcomas, fibrosarcomas, and neurofibrosarcomas (combined) of the integumentary system. These incidences were increased significantly above control rates in the high-dose males by the Incidental Tumor and Fisher Exact tests. Low-dose male mice had significantly increased incidences of lymphoma compared with controls by the Life Table test and Fisher Exact test, but the tests for dose-related trend were not significant because the incidence in high-dose male mice was lower than the incidence in low-dose male mice. This evidence was considered equivocal by NTP (1986), and it is not known whether exposure to isophorone would cause cancer in human.

2.4 LEVELS IN HUMAN TISSUES AND FLUIDS ASSOCIATED WITH HEALTH EFFECTS

No studies were located regarding levels of isophorone or its metabolites in human tissues and fluids associated with effects. Furthermore, no studies were located describing methods for detecting isophorone or its metabolites in human tissues and fluids.

2.5 LEVELS IN THE ENVIRONMENT ASSOCIATED WITH LEVELS IN HUMAN TISSUES AND/OR HEALTH EFFECTS

Although isophorone has been detected in environmental media (see Chapter 5), no data were located allowing associations of effects of isophorone in humans or levels of isophorone or its metabolites in human tissues and fluids with environmental levels of isophorone.

2.6 TOXICOKINETICS

2.6.1 Absorption

2.6.1.1 Inhalation Exposure

No studies were located regarding the rate and extent of absorption of isophorone following inhalation exposure of humans or animals to isophorone. Isophorone was widely distributed to the organs of rats exposed for 4 hours to a concentration of 400 ppm isophorone (Dutertre-Catella 1976), indicating that isophorone is absorbed after inhalation exposure. That isophorone is absorbed by the lungs can also be inferred from the systemic toxicity observed in animals following inhalation exposure (see Section 2.2.1.2 on systemic effects following inhalation exposure). Imbriani et al. (1985) measured a blood/air partition coefficient of 2349 for isophorone, indicating that isophorone is absorbed readily from the lungs.

2.6.1.2 Oral Exposure

No studies were located regarding the absorption of isophorone in humans following oral exposure.

Preliminary results of a pharmacokinetic study indicate that rats treated orally with ^{14}C-isophorone excreted 93% of the radiolabel in the urine, expired air, and feces in 24 hours (Strasser 1988). The majority was found in the urine indicating that isophorone was well absorbed. The wide distribution of isophorone in the organs of rats and a rabbit 1-5 hours after dosing by gavage with 4000 mg/kg (Dutertre-Catella 1976) indicates rapid gastrointestinal absorption. In two rabbits given a gavage dose of 1000 mg/kg isophorone, a blood level of isophorone of 102 μg/L was found within 10 minutes. The level increased to 141 μg/L in 30 minutes and declined to $\leq$0.05 μg/L in 21 hours. The results indicate rapid absorption and elimination. The detection of unchanged isophorone and its metabolites (see Section 2.6.3 on Metabolism) in the urine and the observations of systemic toxicity and carcinogenicity (see Section 2.2.2 on effects of oral exposure) in animals exposed orally to isophorone provide qualitative evidence that isophorone is absorbed after oral exposure.

2.6.1.3 Dermal Exposure

No studies were located regarding the absorption of isophorone following dermal exposure of humans or animals. A report that a high dermal dose resulted in signs of CNS depression in 1/4 rabbits suggests that isophorone is absorbed dermally (Hazleton Labs 1964), but other systemic effects have not been described.

2.6.2 Distribution

2.6.2.1 Inhalation Exposure

No studies were located regarding the distribution of isophorone following inhalation exposure of humans.

In rats exposed to 400 ppm isophorone for 4 hours and sacrificed immediately after exposure or 1.5 or 3 hours after exposure, levels of isophorone were highest in all tissues examined (brain, lungs, heart, stomach, liver, spleen, pancreas, kidney, adrenals, testicles, and ovaries) immediately after exposure (Dutertre-Catella 1976). Levels ranged from 1.5 to 74 μg/g tissue wet weight. The levels declined rapidly in males but declined very little in females by 3 hours after exposure.

2.6.2.2 Oral Exposure

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

Radiolabel was widely distributed in male rats 24 hours after an oral dose of ^{14}C-isophorone in corn oil, with highest levels in the liver, kidney, preputial gland, testes, brain, and lungs (Strasser 1988). Isophorone was widely distributed to the tissues of rats and a rabbit following treatment with isophorone at a gavage dose of 4000 mg/kg (Dutertre-Catella 1976). The rats died within 1-5 hours and the rabbit died within an hour after dosing at which times the tissues were sampled for analysis. In rats, tissue levels of isophorone in μg/g tissue wet weight were as follows: stomach - 6213, pancreas - 2388, adrenals - 1513, spleen - 1038, liver - 613, brain - 378, lung - 383, heart - 387, kidney - 465, testes - 275, and ovaries - 471. In the rabbit, tissue levels were as follows: stomach - 5395, adrenals - 1145, ovaries - 3000, spleen - 545, liver - 515, kidney - 295, heart - 260, and lungs - 50.

2.6.2.3 Dermal Exposure

No studies were located regarding the distribution of isophorone following dermal exposure of humans or animals.

2.6.3 Metabolism

No studies were located regarding the metabolism of isophorone in humans following exposure to isophorone by any route.

Rabbits and rats treated orally with isophorone excreted unchanged isophorone in the expired air and in the urine (Dutertre-Catella et al. 1978; Truhaut et al. 1970). The urine also contained 3-carboxy-5,5-dimethyl-2-cyclohexene-1-one and glucuronic conjugates of 3,3,5-trimethyl-2-cyclohexene-1-ol (isophorol), 3,5,5-trimethylcyclohexanone

(dihydroisophorone), and cis- and trans-3,5,5 trimethylcyclohexanols. Rat urine contained more dihydroisophorone and less isophorol than did rabbit urine. Dutertre-Catella et al. (1978) proposed that metabolism of isophorone involves methyloxidation to 3-carboxy-5,5-dimethyl-2-cyclohexene-1-one, reduction of the ketone group to isophorol, reduction of the ring double bond to dihydroisophorone, and dismutation of dihydroisophorone to cis- and trans-3,5,5-trimethylcyclohexanols. The metabolic pathways are presented in Figure 2-3.

2.6.4 Excretion

2.6.4.1 Inhalation Exposure

No studies were located regarding the excretion of isophorone or its metabolites following inhalation exposure of humans to isophorone. Dutertre-Catella (1976) found that the excretion of isophorone in air was low (110 μg) and declined further to 30 μg at 2.5-3 hours after exposure of rats to 400 ppm for 4 hours.

2.6.4.2 Oral Exposure

No studies were located regarding the excretion of isophorone or its metabolites following oral exposure of human to isophorone.

Rats and rabbits excreted unchanged isophorone and metabolites in the urine and unchanged isophorone in the expired air following oral dosing with isophorone (Dutertre-Catella et al. 1978), but the rate and extent of excretion were not reported. Preliminary results of a pharmacokinetic study indicate that following an oral dose of ^{14}C-isophorone, male rats excreted 93% of the radiolabel in the urine, feces, and expired air in 24 hours, with the majority in the urine (Strasser 1988).

2.6.4.3 Dermal Exposure

No studies were located regarding the excretion of isophorone or its metabolites following dermal exposure of humans or animals.

2.7 INTERACTIONS WITH OTHER CHEMICALS

The possible synergistic interactions of isophorone with other solvents are important because mixed exposures occur in occupational settings and may occur in the environment. The joint toxicity of isophorone with 26 other industrial liquid chemicals based on determinations of the oral LD_{50}s in rats of each chemical alone and in a 1:1 (v/v) mixture was determined (Smyth et al. 1969). The LD_{50}s of the mixtures were predicted based on the assumption of additivity of the LD_{50}s of each component, and the ratios of the predicted values to experimentally determined values were calculated. Greater than additive toxicity was observed for the mixtures of isophorone with nine chemicals: tetrachloroethylene, propylene glycol,

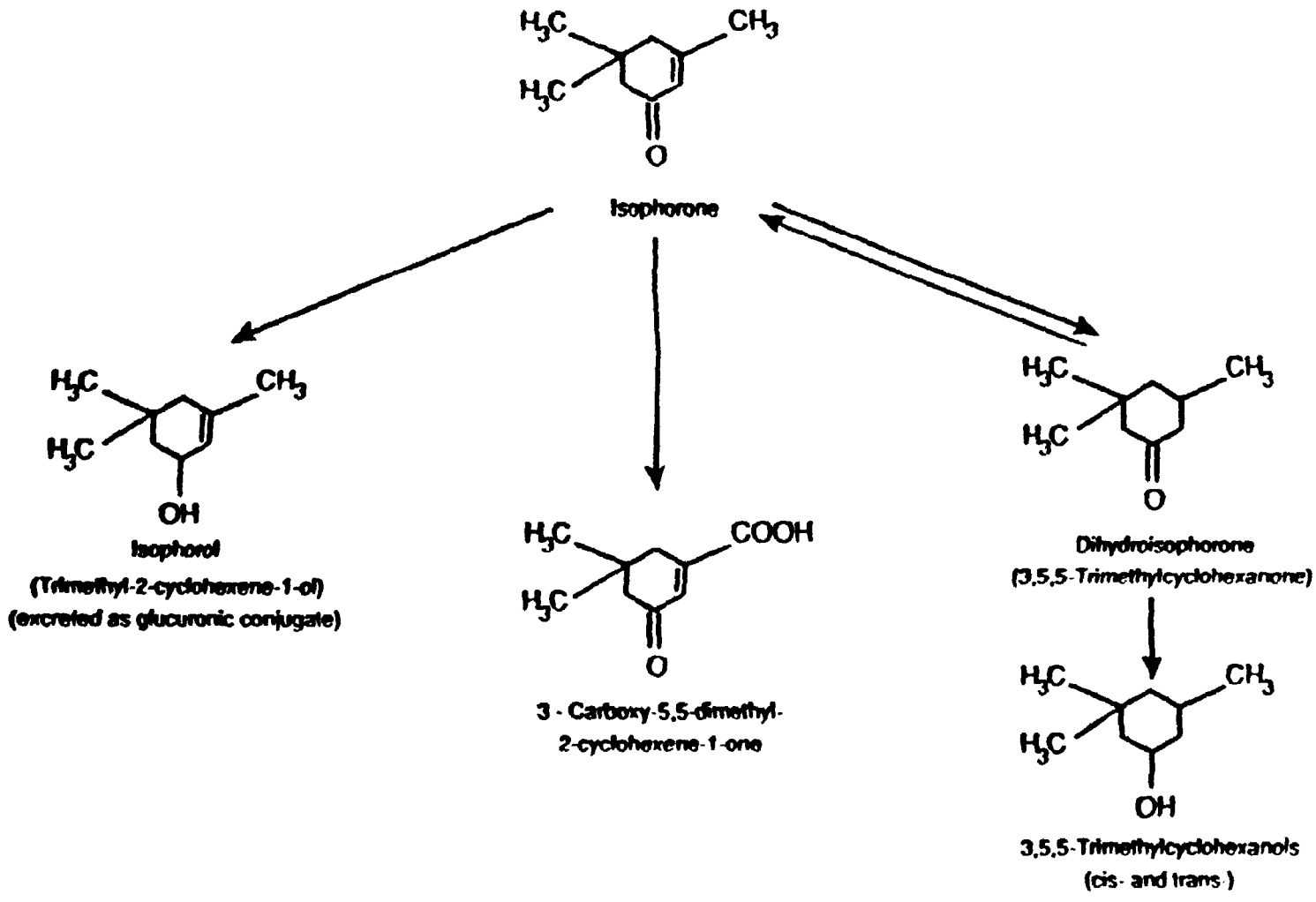


FIGURE 2-3. Metabolic Scheme for Isophorone

Source: Duterte-Catella et al. 1978.

morpholine, ethyl alcohol, ethyl acetate, carbon tetrachloride, acrylonitrile, acetonitrile, and acetone. Less than additive toxicity was observed for the mixtures of isophorone with 17 chemicals: Ucon LB-250, Ucon 50-HB-260, toluene, Tergitol XD, propylene oxide, polyethylene glycol 200, Phenyl Cellosolve, nitrobenzene, acetophenone, aniline, Butyl Cellosolve, butyl ether, diethanolamine, dioxane, ethyl acrylate, ethylene glycol, and formalin. When the frequency distribution of the ratios for all combinations of all chemicals were adjusted to give a normal distribution, however, none of the ratios for mixtures with isophorone deviated significantly from the mean ratios, indicating essentially additive toxicity. In a subsequent study, the additivity of equitoxic mixtures, defined as a mixture of chemicals in volumes directly proportional to their oral LD_{50} in rats, was determined (Smyth et al. 1970). Isophorone showed less than additive toxicity with Phenyl Cellosolve and Ucon Fluid 50-HB-260, and greater than additive toxicity with propylene oxide. The mechanism for such interactions is not known.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

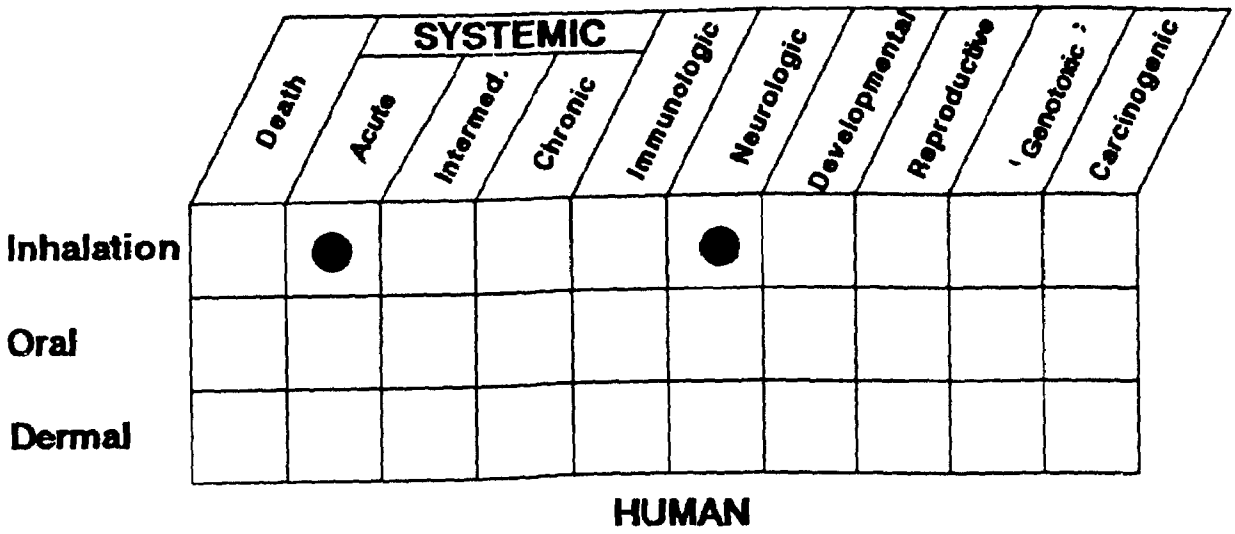
Isophorone produced kidney effects in male rats in the NTP (1986) study. Strasser (1988) found that isophorone caused protein droplet formation in the kidneys of male rats, suggesting that isophorone can induce protein nephropathy. Alden (1986) discussed the possibility that proteinuric humans and humans with low molecular weight protein nephropathy, such as people with multiple myeloma (Bence-Jones protein) or mononuclear cell leukemia (lysozyme), may be more susceptible to chemically-induced protein nephropathy. He concluded, however, that this syndrome is probably specific to the male rat.

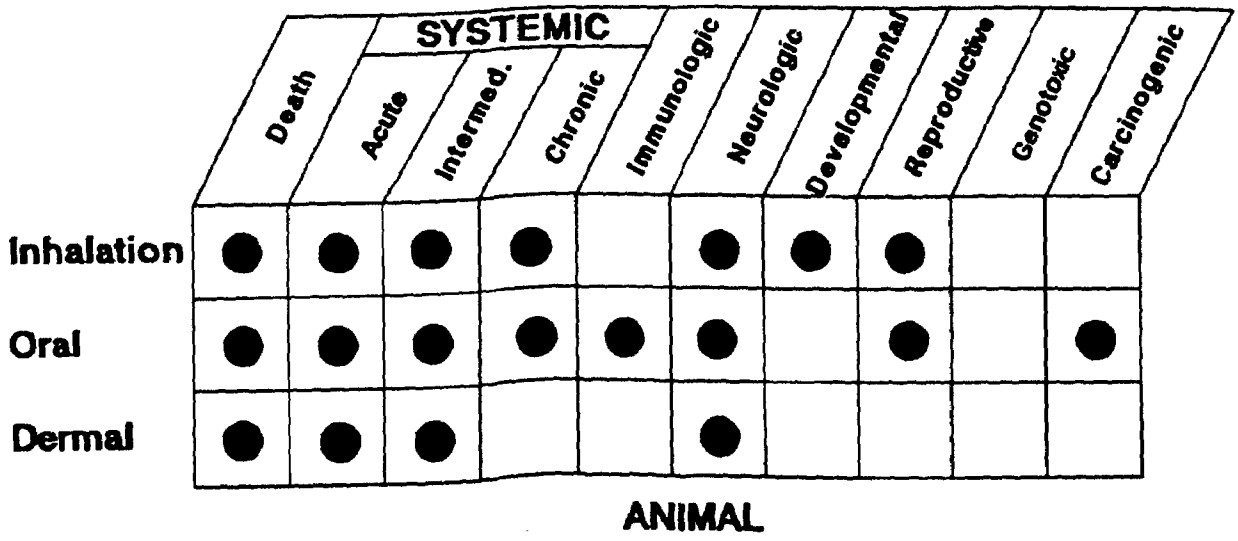
2.9 ADEQUACY OF THE DATABASE

Section 104 (i) (5) of CERCLA, 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 isophorone is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

2.9.1 Existing Information on Health Effects of Isophorone

As seen from Figure 2-4, very little information is available regarding the health effects of exposure of humans to isophorone.





● Existing Studies

FIGURE 2-4 Existing Information on Health Effects of Isophorone

Experimental studies in humans have attempted to determine the inhalation thresholds for odor detection and eye, nose, and throat irritation. Reports on humans occupationally exposed to isophorone also indicate that isophorone is irritating to the skin, eye, nose, and throat, and may cause symptoms of dizziness, fatigue, and malaise.

Data are available for acute and intermediate inhalation exposures that have resulted in death of animals. These exposures also produced signs of central nervous system toxicity, lung irritation, possible kidney damage, and possible hematological changes and growth depression. Chronic inhalation exposure of rats and rabbits resulted in mild liver effects. Inhalation exposure of pregnant rats and mice during gestation did not result in fetotoxic or teratogenic effects at concentrations up to 115 ppm, but results at 150 ppm are difficult to interpret. No information was available on the effects of chronic inhalation exposure.

Data are available for oral doses associated with death and increased mortality in acute, intermediate, and chronic exposure. Acute and intermediate oral studies have also produced signs of central nervous system toxicity at high doses during exposure. In intermediate duration studies of oral exposure of animals to isophorone, comprehensive histological examination of tissues and organs found no effects. Chronic oral exposure of mice resulted in hyperkeratosis of the forestomach, non-neoplastic liver lesions, and equivocal evidence of liver tumors, integumentary system tumors, and malignant lymphomas. Chronic oral exposure of rats resulted in hyperplastic and neoplastic kidney lesions and preputial gland carcinomas.

Application of isophorone to the skin of animals results in skin irritation, and application to the eye results in severe eye damage. There is some information that dermal exposure of rabbits causes signs of neurotoxicity at high doses. This could indicate that isophorone is absorbed dermally, but other systemic effects have not been described.

No studies of the genotoxic effects of oral, inhalation, or dermal exposure to isophorone were found, but studies in bacteria and mammalian cells indicate that isophorone is at best weakly genotoxic.

2.9.2 Data Needs

Single Dose Exposure. Studies of single inhalation, oral, or dermal exposure of rats, guinea pigs, and mice have provided data on lethal and non-lethal levels of isophorone and levels producing signs of neurotoxicity. Single-dose dermal and ocular studies in animals have demonstrated that isophorone is irritating to the skin and eyes. Gross clinical and necropsy observations have been made, but no reliable single-dose study examined the internal tissues of animals histologically or attempted to identify dose-response data for more subtle systemic toxic effects. Such studies might provide information on the mechanisms of lethality and neurotoxicity, as

well as information on the thresholds for systemic toxicity due to single dose exposure.

Repeated Dose Exposure. Repeated inhalation exposure studies of isophorone conducted in rats and guinea pigs by Smyth et al. (1942) reported severe respiratory and kidney lesions, but this study was criticized by Rowe and Wolf (1963) for using impure isophorone and overestimating the concentrations. Furthermore, dose-response data were poorly reported and results in rats and guinea pigs were reported together. A study by Hazleton Labs (1968) suggested hematological and liver weight effects in rats, but only one exposure concentration was used. A 4-6 month inhalation study in rats reported ocular and nasal irritation but no exposure-related effects on lungs or livers (Dutertre-Catella 1976). Results were poorly reported and only one concentration was used. A well-conducted subchronic inhalation study that uses several concentrations of pure isophorone and monitors for clinical signs, hematological and biochemical changes, and gross and histopathological changes in animals would provide dose-response data for toxicological endpoints and remove uncertainties associated with the study by Smyth et al. (1942). Well-conducted, repeated-dose oral studies in rats, mice, and dogs at several dosage levels including maximum tolerated doses produced no systemic effects. A 2-week dermal study in rabbits revealed no biochemical evidence of liver damage (Dutertre-Catella 1976), but other indices of toxicity were not examined. An 8-week dermal study in rats revealed erythema and scar tissue formation, which disappeared after exposure ceased (Dutertre-Catella 1976). As screen printers are repeatedly exposed dermally to isophorone and the extent of dermal absorption is not known, better repeated dermal dose studies examining systemic toxicity in animals might provide information on whether repeated dermal exposure of humans poses a threat of toxic potential.

Chronic Exposure and Carcinogenicity. Well-conducted chronic oral studies provide information on the systemic and carcinogenic effects of isophorone in rodents. In a chronic oral study, male rats exposed to isophorone developed kidney and preputial gland tumors. The relevance of these tumors in male rats to humans has been questioned; therefore, additional research to clarify the relevance is desirable. Indeed, on-going studies are being conducted (see Section 2.9.3). In a chronic inhalation study, rats and rabbits had ocular and nasal irritation and slight liver effects (Dutertre-Catella 1976), but few animals and only one concentration were used. No chronic dermal studies were located. It is not possible to predict that effects following chronic inhalation or dermal exposure to isophorone would be similar to those following chronic oral exposure, partially because the pharmacokinetic disposition of isophorone has not been compared for the three routes of exposure. Available toxicokinetic data (see Section 2.6) indicate that isophorone is metabolized to dihydroisophorone, isophorol, and other products after oral dosing of rats and rabbits, but different metabolic pathways may operate following inhalation and dermal exposure. Differences in absorption and tissue

distribution among the three routes of exposure could also account for differences in toxic response. Chronic inhalation and dermal studies in animals might provide dose-response data on the systemic effects that could be related to possible systemic effects of inhalation and dermal exposure of humans. Long-term exposure of humans to isophorone by inhalation and by skin contact occurs in occupational settings.

Genotoxicity. The available genotoxicity studies (Salmonella/microsome assays, mutations in mouse lymphoma cells, tests of unscheduled DNA synthesis, sister chromatid exchange, and chromosome aberrations in cultured mammalian cells, and an in vivo micronucleus tests) indicate that isophorone may be weakly genotoxic. Additional genotoxicity tests would add to the rather limited data base on genotoxicity, but probably would not change the conclusion that isophorone in weakly genotoxic.

Reproductive Toxicity. An intermediate duration study examined only the pregnancy rate and litter size in rats exposed to isophorone by inhalation for 3 months before mating. Histological examination of reproductive organs of rats, mice, and dogs exposed orally to isophorone in subchronic and chronic studies indicate no treatment-related lesions, but multigeneration or continuous breeding studies have not been conducted. Such studies would provide further information regarding the reproductive effects of isophorone in animals, which may then be related to possible reproductive effects in humans.

Developmental Toxicity. Developmental studies by the inhalation route in rats indicated growth retardation in the rat fetuses at a concentration of 115 ppm, and maternal toxicity at all concentrations tested ($\geq$25 ppm). Exencephaly was seen in several rat and mouse fetuses after exposure of the dams to 150 ppm during the organogenesis period. The developmental effects following oral or dermal exposure have not been studied. It is not known whether isophorone crosses the placenta, but there is no reason to assume that it would not do so. Further developmental studies in animals by relevant environmental routes, such as drinking water and diet, would provide information on possible fetotoxic and teratogenic effects in animals that might be relevant to humans. Studies in drinking water and diet are particularly relevant because isophorone has been detected in groundwater, ambient water, drinking water, oysters, and cranberries (see Section 5.4 on environmental monitoring).

Immunotoxicity. No histopathological effects on immunological organs and tissues of animals were found in subchronic and chronic oral studies, but a battery of immunotoxicity tests has not been performed. Such tests provide a more sensitive assessment of possible immunotoxic effects than do histological examinations of tissues and organs of the immunological system. Isophorone is a skin irritant in rabbits, guinea pigs, and humans, but it has not been tested for sensitization. Such tests might provide information on whether an allergic response to isophorone is likely. The potential for

dermal contact by humans occurs in occupational settings and in soil at waste sites.

Neurotoxicity. No histopathological effects on organs and tissues of the neurological systems of animals were found in subchronic and chronic oral studies, but signs of central nervous system toxicity were reported in inhalation, oral, and dermal studies. A battery of tests for neurotoxicity would provide further information of the neurotoxicity in animals, which then might be related to possible neurotoxic effects in humans.

Epidemiological and Human Dosimetry Studies. The only known health effects of isophorone in humans are eye, nose, and throat irritation, and fatigue and malaise. This information comes from two limited industrial hygiene surveys, two experimental studies in human volunteers, and a communication to the ACGIH. Effects in animals, however, include CNS depression, liver and kidney damage, hyperkeratosis of the forestomach, some evidence of cancer, and suggestive evidence of developmental toxicity. As discussed in Chapter 5, isophorone has been detected in surface water, drinking water, industrial effluents, urban runoff, and water and soil at waste sites. Isophorone has a relatively low vapor pressure (Union Carbide 1968) and high reactivity with hydroxyl radicals (Atkinson 1985, 1987); therefore, exposure to isophorone in the ambient atmosphere distant from the source is unlikely. Indeed, monitoring data for isophorone in air are lacking. Inhalation as well as dermal exposure, however, occurs in occupational settings where isophorone is used as a solvent. Epidemiology studies of people who live in areas where isophorone has been detected in ambient and drinking water, near industries releasing isophorone, or near hazardous waste sites, and of people occupationally exposed, could provide information on whether isophorone produces effects in humans similar to those seen in animals, or other toxic effects.

No studies were located that monitored human tissues for isophorone or its metabolites. Furthermore, analytical methods for the detection of isophorone or its metabolites in humans tissues and fluids were not located. Metabolism studies in rats and rabbits, however, indicated that isophorone, isophorol, dihydroisophorone, 3-carboxy-5,5-dimethyl-2-cyclohexene-1-one, and cis- and trans-3,5,5-trimethylcyclohexanols were excreted in the urine following oral exposure to isophorone (Dutertre-Catella et al. 1978). If isophorone and these or other metabolites can be detected in the urine of humans and be correlated with exposure, it may be possible to monitor humans for exposure. If toxic effects of isophorone are identified in humans, it may then be possible to correlate urinary levels of isophorone or its metabolites with systemic effects.

Biomarkers of Disease. No disease states in humans produced by exposure to isophorone are known. If epidemiological studies are conducted that correlate exposure with diseases, it may be possible to identify subtle changes associated with a particular disease state.

2. HEALTH EFFECTS

Disease Registries. At present, the only known health effects of isophorone in humans are eye, nose, and throat irritation, and fatigue and malaise. If epidemiological studies identify particular diseases produced by isophorone, it may be possible to determine the number of people affected and the factors associated with identifying the disease in certain populations, such as exposure to high levels near hazardous waste sites.

Bioavailability from Environmental Media. No studies were located regarding the bioavailability of isophorone from environmental media. Furthermore, no reports were located indicating that isophorone or its metabolites have been detected in human tissues or fluids. Since the monitoring literature reports that isophorone is present in the environment as well as in environmental organisms, the lack of data does not necessarily indicate a lack of bioavailability. Fish may be the only source of isophorone in the environment that is not subject to large spatial and temporal variations in concentration, as appears to be the case with drinking water. In particular, fish in the Lake Michigan area are known to contain isophorone (Camanzo et al. 1987), and analysis of the body fluids of people who consume the fish may allow a determination of the existence of exposure and an estimation of the degree of exposure.

Food Chain Bioaccumulation. No studies were located regarding the food chain bioaccumulation of isophorone from environmental media. The monitoring literature reports that isophorone is present in the environment as well as in environmental organisms. The monitoring data further suggest that isophorone levels in fish do not correlate well with the lipid content of the fish (see Section 5.4). Thus, structure-activity relationships developed to estimate levels in biological media based on the partitioning properties of a chemical may not provide accurate information for isophorone. Furthermore, only one bioaccumulation study was available. In this study, which indicated a low potential for bioaccumulation, fish were exposed to isophorone in water rather than in food. From these data, it appears that food chain bioaccumulation may be occurring, and a clearer understanding of the potential for this would aid in determining how levels in the environment affect the food chain and potentially impact on human exposure levels.

Absorption, Distribution, Metabolism, Excretion. The only toxicokinetic data of isophorone are the in vivo metabolism studies in rats and rabbits following oral exposure (Dutertre-Catella et al. 1978) and the preliminary disposition data of Strasser (1988). These studies indicate that isophorone is metabolized to dihydroisophorone and isophorol in animals following oral exposure. Different metabolic pathways and patterns of distribution and excretion, however, may operate after inhalation or dermal exposure. Differences in the rate and extent of absorption, metabolic pathways, and disposition may account for differences in the toxicity of a chemical following exposure by different routes. Thus, further studies in animals of the rate and extent of absorption and excretion following exposure by all three routes and of distribution and metabolism following

inhalation and dermal exposure, and in vitro studies to elucidate metabolic pathways would provide the information to fully characterize the pharmacokinetics of isophorone in animals. Ethical considerations limit the testing of humans, but the determination of the urinary excretion of isophorone and its metabolites by humans with known exposure to isophorone (e.g., workers in the printing trades), may provide a means of monitoring humans for exposure.

Comparative Toxicokinetics. The metabolism studies by Truhaut et al. (1970) and Dutertre-Catella et al. (1978) indicated that metabolism of isophorone in rats and rabbits was qualitatively similar, but the proportion of the metabolites excreted was different. Differences in the toxicokinetics of a chemical among species may account for differences in toxic responses. The potential for isophorone to produce toxic effects has been investigated in rats, mice, dogs, guinea pigs, and rabbits, but the animal species that serves as the best model for extrapolating results to humans is not known. Ethical considerations limit the amount of information that can be obtained by testing isophorone in humans, but analysis of the urine of people with known exposure to isophorone for parent compound or metabolites could provide knowledge of the metabolic pathways in humans. Qualitative and quantitative comparison of human metabolites with those of animals could help identify the most appropriate species to serve as a model for predicting toxic effects in humans and studying the mechanisms of action.

2.9.3 On-going Studies

A manuscript of the study demonstrating protein droplet formation in the kidneys of male rats following acute oral exposure to isophorone and of the distribution study by Strasser will be submitted for publication to Toxicology and Applied Pharmacology (Strasser 1988). These studies were presented as a Poster Presentation at the Society of Toxicology meetings in February, 1988, and an abstract (Strasser et al. 1988) has been published. In addition, the manuscript to be submitted to Toxicology and Applied Pharmacology will contain added information on the distribution of radiolabel in female rats and in the preputial gland of male rats (Strasser 1988).

James Swenberg, formerly at the Chemical Industry Institute of Toxicology (CIIT), and his colleagues at CIIT are continuing the investigation of the mechanism of hydrocarbon-induced nephropathy and the induction of renal tumors in male rats (Swenberg et al. 1989). These investigations include isophorone. Swenberg and colleagues are also investigating whether low molecular weight proteins found in humans behave similarly to $\alpha_{2\mu}$-globulin of male F344 rats.

No on-going biomonitoring studies or studies of toxic effects of isophorone in humans were identified.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

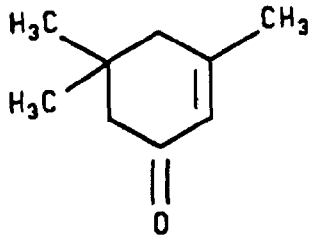
Data pertaining to the chemical identity of isophorone are listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

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

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of Isophorone

	Value	Reference
Chemical Name	2-Cyclohexen-1-one, 3,5,5-trimethyl-	CAS 1988
Synonyms	Isoacetophorone Isoforon 1,5,5-Trimethyl-3-oxocyclohexene	CAS 1988; SANSS 1988
Trade Name(s)	No data	
Chemical Formula	$C_9H_{14}O$	CAS 1988
Chemical Structure		SANSS 1988
Identification Numbers:		
CAS Registry	78-59-1	CAS 1988
NIOSH RTECS	GW7700000	RTECS 1988
EPA Hazardous Waste	No data	
OHM-TADS	7216766	OHM-TADS 1988
DOT/UN/NA/IMCO	No data	
HSDB	619	HSDB 1988
NCI	C55618	HSDB 1988

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

TABLE 3-2. Physical and Chemical Properties of Isophorone

Property	Value	Reference
Molecular weight	138.21	Union Carbide 1968
Color	Water-white	Hawley 1981
Physical state	Liquid	Hawley 1981
Freezing point	-8.1°C	Union Carbide 1968
Boiling point	215.3°C	Union Carbide 1968
Specific gravity, 20/20°C	0.9229	Union Carbide 1968
Odor	Mild	Union Carbide 1968
Odor threshold		
Water	5.4 ppm (w/v)	Amoore and Hautala 1983
Air	0.20 ppm (v/v)	Amoore and Hautala 1983
Solubility		
Water	12,000 mg/L (20°C) 14,500 mg/L (25°C)	Union Carbide 1968 Veith et al. 1980
Organic Solvents	Soluble in ether, acetone, alcohol	Weast 1985
Partition coefficients		
Log octanol/water	1.67 (20°C) (Experimental)	Veith et al. 1980
Log K_{oc}	No data	
Vapor pressure	0.3 mm Hg (20°C)	Extrapolated using data from Union Carbide 1968
Henry's Law constant	4.55×10^{-6} atm-m^3/mol (20°C)	Calculated from vapor pressure and water solubility data
Autoignition temperature	864°F (462°C)	Hawley 1981
Flashpoint, open cup	184°F (84°C)	Dean 1985
Flammability limits	0.8-3.5 vol %	HSDB 1988
Conversion factors		
ppm (v/v) to mg/m^3 in air (20°C)	ppm (v/v) x 5.75 = mg/m^3	
mg/m^3 to ppm (v/v) in air (20°C)	mg/m^3 x 0.174 = ppm (v/v)	

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

According to the most recent edition of the United States International Trade Commission publication on U.S. production and sales of synthetic organic chemicals (USITC 1987), Union Carbide (Institute, WV), is the only domestic manufacturer of isophorone. A comparison of the list of isophorone manufacturers in USITC (1987) and USITC (1986) shows that Exxon Corporation (Bayway, NJ) also manufactured this chemical, but discontinued production in 1985. Because of the limited number of domestic manufacturers of isophorone and their desire to maintain confidentiality, up-to-date information regarding the production volume of isophorone in the U.S. is not available. In 1973, 35 million pounds of isophorone were produced in the United States (Papa and Sherman 1981) and in 1980, approximately 20-30 million pounds were produced (CMA 1981). The decrease may be because of replacement of isophorone with less costly solvents (CMA 1981).

Isophorone can be prepared by (1) passing acetone vapor over a catalyst bed of magnesium aluminate, zinc oxide-bismuth oxide, or calcium oxide under pressure at 300-400°C or (2) reacting acetone, water (up to 30%), and potassium hydroxide (≈1%) in a column under a pressure of about 35 atm and at a temperature of about 200°C (Papa and Sherman 1981). Commercial isophorone usually contains some unconjugated isomer (up to 5%) and small amounts (<1%) of xylitone (Papa and Sherman 1981). Isophorone tends to discolor on prolonged storage; stabilization against color formation can be provided by treatment with p-toluenesulfonic acid, acidified Fuller's earth, diazines, or diisopropylamine (Papa and Sherman 1981).

4.2 IMPORT

During 1984, 2,158 million pounds of isophorone were imported into the United States (HSDB 1988).

4.3 USE

Isophorone is a solvent for a large number of natural and synthetic polymers, resins, waxes, fats, and oils. Specifically, it is used as a solvent for concentrated vinyl chloride/acetate-based coating systems for metal cans, other metal paints, nitrocellulose finishes, printing inks for plastics, some herbicide and pesticide formulations, and adhesives for plastics, poly(vinyl) chloride and polystyrene materials (Papa and Sherman 1981). Isophorone also is an intermediate in the synthesis of 3,5-xylenol, 3,3,5-trimethylcyclohexanol (Papa and Sherman 1981), and plant growth retardants (Haruta et al. 1974). Of the total production, 45-65% is used in vinyl coatings and inks, 15-25% in agricultural formulations, 15-30% in miscellaneous uses and exports, and 10% as a chemical intermediate (CMA 1981).

4.4 DISPOSAL

Isophorone may be disposed of by incineration, wastewater treatment, or sanitary landfill (OHM-TADS 1988).

4.5 ADEQUACY OF THE DATABASE

Section 104 (i) (5) of CERCLA, 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 isophorone is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

4.5.1 Data Needs

Production, Use, Release, and Disposal. Industrial production methods for isophorone are well described in the literature (including the patent literature) and there does not appear to be a need for further information in this area. Uses of isophorone are documented, but a recent detailed breakdown of the percentage of production consumed by each use category is lacking. There is also a lack of data regarding the presence of isophorone in retail products, such as paints and paint thinners. This information, which is useful for estimating the potential for environmental releases from various industries as well as the potential environmental burden, is difficult to obtain in detail since it is considered confidential business information for those industries that manufacture isophorone. Release information is similar to use information in that it is not easily obtained and can be used to estimate environmental burdens and potentially exposed populations. According to the Emergency Planning and Community Right to Know Act of 1986 (EPCRTKA), (§313), (Pub. L. 99-499, title III, §313), industries are required to submit release information to the EPA. The Toxic Release Inventory (TRI), which contains release information for 1987, became available in May of 1989. This database will be updated yearly and should provide a more reliable estimate of industrial production and emission. Disposal information is useful for determining environmental burden and potential sources of high environmental exposures. There is a lack of data on current disposal practices for this chemical.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Isophorone is released to the air mainly in urban centers, as a result of evaporation of solvents containing this chemical. Isophorone can enter surface waters from industrial effluent discharges or from runoff from soils at hazardous waste or other contaminated sites. Isophorone disappears rapidly in air by hydroxyl radical reaction (half-life <5 hours), but may persist in natural waters from several days to about a month. Volatilization and sorption are not expected to be significant removal mechanisms from water. In soils, isophorone is expected to degrade microbially, but no rate data are available. Isophorone has been monitored in effluents (range <5-1380 ppb), ambient water (range <0.6-100 ppb), drinking water (from contaminated surface water) (range 0.02-9.5 ppb), and soils at hazardous waste sites (range 0.16-6500 ppm). At this time, isophorone has been found in at least 9 out of 1177 National Priority List (NPL) hazardous waste sites in the United States (VIEW database 1989). Occupational exposures occur mainly by inhalation and dermal contact and are documented most frequently in the printing trades. Air concentrations in screen printing facilities range from <0.47-25.7 ppm. A 1988 estimate by the National Institute for Occupational Safety and Health reported that 37,469 workers (9211 of whom were female) were exposed to isophorone in both trade name products and chemical named products.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Since isophorone is used mainly as a solvent (see Subsection 4.3) that is evaporated during or after use, the vast majority of environmental releases are to the air. Use patterns indicate that most air releases are in urban centers, with a smaller percentage of release in rural areas. Nonetheless, very little ambient air monitoring data exist to confirm this, probably because of its short atmospheric lifetime (half-life <5 hours). Apparently, a major source of isophorone in the environment is the printing industry, since these operations usually do not use emission control technologies to reduce emitted isophorone concentrations (Bierbaum and Parnes 1974; Kominsky 1981; Lee and Frederick 1981; Samimi 1982). Other industries e.g. metal coating that use similar ventilation methods (NIOSH 1978a) are major sources of atmospheric isophorone. Coal-fired power plants may also emit isophorone to the air, since isophorone has been detected in the fly ash of one such plant (Harrison et al. 1985).

Volatilization from surface waters is not expected to be a significant source of isophorone in the atmosphere, since this is anticipated to be a slow process (based on the Henry's Law Constant of 4.55×10^{-6} atm m^3 mol^{-1}). Wastewater treatment plants may, however, emit some isophorone from influent

water to the air, particularly if gas stripping methods are used (Hawthorne and Sievers 1984, Hawthorne et al. 1985). Drinking water plants that practice aeration of influent water may also emit small amounts of isophorone to air.

5.2.2 Water

Little data are available to estimate releases of isophorone to water. During isophorone manufacture, process water may contact the isophorone and carry some of it to wastewater streams. During use of isophorone, paint spray booths that use water curtains, wash water, and process water all may contain isophorone. Isophorone has been detected in the United States in industrial effluent discharges (Bursey and Pellizzari 1982; Hawthorne and Sievers 1984; Hawthorne et al. 1985; Jungclaus et al. 1976), hazardous waste landfill leachate and runoff (Ghassemi et al. 1984; Hauser and Bromberg 1982; Stonebraker and Smith 1980), and urban runoff (Cole et al. 1984). Specific industrial categories that produce wastewaters containing isophorone include timber products, petroleum refining, paint and ink, pulp and paper, automobile and other laundries, pharmaceuticals, foundries, transportation equipment, and publicly-owned treatment works (Bursey and Pellizzari 1982). It is likely that treated waters from these industries that are often discharged to surface waters will contain isophorone (Bursey and Pellizzari, 1982).

5.2.3 Soil

The only direct measurements of isophorone in soil were found for samples taken from hazardous waste sites. Ghassemi et al. (1984) found isophorone in leachates from hazardous waste landfills, and Hauser and Bromberg (1982) detected the presence of isophorone in the "sediment/soil/water" of Love Canal. These studies suggest that isophorone also was present in the soil. The Contract Laboratory Program Statistical Data Base (queried April 13, 1987) reported that isophorone has been detected at 4 of 357 hazardous waste sites at a concentration range of 1.68-6500 ppm.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Isophorone has a water solubility of 12,000 ppm, a log octanol/water partition coefficient of 1.67, a Henry's Law constant of 4.55×10^{-6} atm m^3 mol^{-1}, a vapor pressure of 0.3 mm Hg at 20°C, a log sediment sorption coefficient of approximately 1.46, and a log bioconcentration factor (BCF) of 0.85. Isophorone is released to air and water from its manufacturing and use. Based on its water solubility, some isophorone may wash out of the atmosphere; however, only limited amounts will be washed out because of the short atmospheric half-life of isophorone. Particularly during the day,

when hydroxyl radical (HO·) concentrations are highest, very little atmospheric transport will occur due to its fast reaction with HO·.

In water, neither volatilization nor sorption to sediments is expected to be an important transport mechanism. The results of two EXAMS model runs and the value of the Henry's Law constant (calculated from the solubility and the vapor pressure) suggest that volatilization will not be important in shallow ponds or in lakes. EXAMS is an environmental model that predicts the behavior of a chemical in surface waters (EPA 1985a). Using the code test data for a pond developed by the Athens Environmental Research Laboratory of EPA, the half-life for volatilization was calculated to be 104 days, while for a lake, the half-life was calculated to be 288 days. Input data included molecular weight, vapor pressure, Henry's Law constant, octanol/water partition coefficient, sediment sorption coefficient, and water solubility. Equations correlating solubility or octanol/water partition coefficients with sorption partition coefficients (K_{oc}) were not developed using structures similar to isophorone, however, and the K_{oc} value entered into the EXAMS model thus should be viewed as tentative. The volatilization rates predicted by the EXAMS model appear to be consistent with the observation of Hawthorne and Sievers (1984), who reported that isophorone could be analyzed in wastewater by purge and trap methods but was not found in the air above the wastewater in a closed system without a purge.

McFall et al. (1985) reported isophorone concentrations in sediments of Lake Pontchartrain, LA, an estuary located in the Mississippi River delta. Sediments containing isophorone were detected in the Inner Harbor Navigation Canal (IHNC), the Rigolets, and the Chef Menteur Pass. Concentrations in the overlying waters were not reported. Therefore, the sorption partition coefficient in these sediments could not be derived from these experimental data.

The bioconcentration of isophorone in bluegill sunfish has been reported by Barrows et al. (1978, 1980) and Veith et al. (1980) (all reports used the same BCF value). These researchers reported a bioconcentration factor of 7 (log BCF = 0.85) as determined in a continuous-dilution flow-through system using ^{14}C-labeled isophorone. This value suggests that concentrations of isophorone in fish living in isophorone-contaminated waters will not be more than an order of magnitude higher than concentrations in the water. Nonetheless, concentrations of isophorone have been found in fish in Lake Michigan tributaries and embayments (Camanzo et al. 1987) (see section 5.4) at concentrations ranging from below the detection limit (≈0.02 mg/kg) to 3.61 mg/kg wet weight. McFall et al. (1985) also analyzed oysters from the IHNC and clams from the Rigolets and the Chef Menteur Pass in Lake Pontchartrain for isophorone. Oysters from the IHNC had detectable levels of isophorone (38 ppb dry weight), but clams did not; the detection limits were not specified and no BCF can be calculated with the data supplied. These data indicate, however, that isophorone can be found in aquatic organisms at mg/kg levels, although no

correlation was found between the concentration of isophorone and lipid content in the organism (Camanzo et al. 1987).

5.3.2 Transformation and Degradation

5.3.2.1 Air

No studies were located regarding the rates or products of reaction of isophorone in the atmosphere. Isophorone does not significantly absorb light above wavelengths of 290 nm (Sadtler Index 1966 [UV #44]); hence, it is not expected to undergo direct photolysis. However isophorone can react with photochemically produced NO_x in the atmosphere (usually formed at higher concentrations in photochemical smogs) producing moderate eye irritation, NO_2, other oxidants (including ozone, various peroxy compounds, and free radicals), and formaldehyde as indicated in smog chamber studies (Altshuller and Bufalini 1971; Farley 1977; Levy 1973). Probably, the most significant reaction of isophorone in the atmosphere is its reaction with HO·
Addition of HO will occur at the double bond of the compound and may be followed by multiple reaction pathways (Atkinson 1985). Recently, Atkinson (1987) developed a method to estimate the HO· reaction rate based on structure. Using this method, an overall reaction rate of 81.5×10^{-12} cm^3 $molecule^{-1}$ sec^{-1} was calculated. This reaction rate yields a half-life of 4.7 hours for an atmospheric 24-hour average HO· concentration of 0.5×10^6 molecules cm^{-3} (Atkinson 1985). In indoor air, HO· concentrations probably are significantly lower (Atkinson 1985); therefore, reaction half-lives of HO· with isophorone in indoor air probably will be much longer than in outdoor air. Thus, isophorone is expected to persist much longer in indoor air than in outdoor air unless the indoor/outdoor air exchange rate is high.

5.3.2.2 Water

The aerobic biodegradation of isophorone has been studied using sludge and wastewater inocula as well as combined biological and physical treatment methods. Isophorone appears to biodegrade under most conditions simulating those in sewage treatment plants. No studies regarding biodegradation or abiotic reactions involving photolysis or oxidation of isophorone in surface and groundwater were located in the literature.

Aerobic biodegradation of isophorone appears to be possible in sewage sludge or settled domestic wastewater. The exact conditions, however, appear to be important. For example, Tabak et al. (1981a,b) reported 100% degradation of isophorone in 7 days using settled domestic wastewater amended with 5 ppm of yeast extract. Price et al. (1974) reported that the equivalent of 42% theoretical oxygen demand for the compound was consumed in 20 days with a domestic wastewater seed without the yeast extract, and Kawasaki (1980) reported that isophorone was resistant to biodegradation in a test developed by the Japanese Ministry of International Trade and Industry (MITI). The MITI test is essentially a BOD test conducted over 14 days with a seed obtained from soil and sludge samples taken throughout

Japan. The results are reported as a pass if 30% or more of the theoretical BOD is consumed and as a fail if less than 30% is consumed. During the operation of two model sewage treatment plants, Hannah et al. (1986) and McShane et al. (1987) reported that virtually all of the isophorone added to the influent water was removed during the activated sludge portion of the treatment process. The hydraulic detention times for both systems were on the order of several hours. None of the test concentrations were near the activated sludge EC_{50} of 100 ppm (Yoshioka et al. 1986). Some of the removal may have been due to adsorption to the sludge as Hannah et al. (1986) reported that the sludge from their process contained isophorone at concentrations that exceeded the influent water concentrations.

While the evidence presented in the literature cited above suggests that isophorone can be virtually completely removed under sewage treatment plant conditions, monitoring data presented in Section 5.4 indicate that isophorone is still present in treated wastewater and in ambient water. This, in turn, suggests that the exact conditions under which isophorone is rapidly biodegraded or removed are not well understood. The presence of this compound in treated wastewater is indicative that the proper removal conditions were not employed for these systems, or that the input concentrations into sewage treatment plants were high enough that the capacity of the treatment plants were exceeded.

5.3.2.3 Soil

No studies were located regarding the transformation of isophorone in soils. Based on the information presented above and the lack of any monitoring data that report isophorone in groundwater or soils (except for hazardous waste sites), it appears that isophorone may not be discharged to soils in large amounts, and the small amounts that are deposited may degrade rapidly in soil. Another explanation, however, is that there is a lack of studies determining isophorone content in soil.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

No ambient air monitoring for isophorone was located in the literature. The estimated atmospheric half-life of isophorone is <5 hours may account for the lack of monitoring data, since concentrations will decrease rapidly with distance from the source. Another explanation, however, is that no studies have been conducted that analyzed for isophorone in air.

5.4.2 Water

Isophorone has been detected in surface waters, sediments, drinking water, industrial effluents, urban runoff, and in runoff waters from hazardous waste sites. Table 5-1 summarizes the available data.

TABLE 5-1. Detection of Isophorone in Water

Media Type	Location	Sampling Dates	# of Samples	Sample Type	Analytical Method	Concentration Range (ppb)	Concentration Mean	% Occurrence	Reference
Surface Water									
	Delaware River	8/77-3/78	NS	grab/ composite	GC/MS	<0.6-3	NS	NS	Hites 1979
	Delaware River	winter '76-'77	18	grab	GC/MS	trace	NS	NS	Sheldon and Hites 1978
	Delaware River	summer '76	18	grab	GC/MS	ND	ND	NA	Sheldon and Hites 1978
	Olentangy River, OH	NS	NS	grab	GC/FID	<5	ND	0	Shafer 1982
	Potomac River by Quantico	1986	NS	grab	GC/MS	<2	ND	0	Hall et al. 1987
Sediments									
	Lake Pontchartrain	5/80-6/80	10	grab	GC/MS	0.9[a]-12	2.9	NS	McFall et al. 1985
Drinking Water									
	Cincinnati, OH	NS	NS	NS	NS	0.02	NS	NS	EPA 1975
	New Orleans, LA	8/74-9/74	NS	continuous adsorption	GC/MS	1.5-9.5	NS	NS	EPA 1974 Keith et al. 1976
	Philadelphia, PA	2/75-1/77	12	grab	GC/MS	NS	NS	17	Suffet et al. 1980
Effluents									
	Shale oil sites	7/81-12/82	NS	grab	GC/MS	0.34-5.8[b]	NS	100	Hawthorne and Sievers 1984
	Tire manufacturing plant	NS	NS	grab	GC/MS	40	NS	100	Jungclaus et al. 1976
	Unspecified effluent	NS	NS	NS	GC/MS	NS	NS	NS	Perry et al. 1979
	Philadelphia sewage treatment plnt influent	8/77-3/78	NS	grab/ composite	GC/MS	100	NS	NS	Hites 1979
	Philadelphia sewage treatment plnt effluent	8/77-3/78	NS	grab/ composite	GC/MS	10	NS	NS	Hites 1979
	Plastics effluents	NS	NS	grab	GC/FID	40.5	NS	100	Shafer 1982
	Ship holding tank	NS	NS	grab	GC/FID	<50	NS	0	Shafer 1982
	Secondary sewage effluent	NS	NS	grab	GC/FID	120	NS	100	Shafer 1982
	Chemical industry final effluent	NS	NS	grab	GC/FID	<5	NS	0	Shafer 1982
	Chemical manufacturing plant final effluent	NS	NS	grab	GC/FID	< 20	NS	0	Shafer 1982
	Timber products	NS	2[c]	NS	GC/MS	55-111	83	NS	Bursey and Pellizzari 1982
	Petroleum refining	NS	1[c]	NS	GC/MS	1380	NS	NS	Bursey and Pellizzari 1982
	Paint and ink	NS	5[c]	NS	GC/MS	26-946	185	NS	Bursey and Pellizzari 1982
	Pulp and paper	NS	1[c]	NS	GC/MS	753	NS	NS	Bursey and Pellizzari 1982
	Auto & other laundries	NS	2[c]	NS	GC/MS	43-44	43	NS	Bursey and Pellizzari 1982

TABLE 5-1 (continued)

Media Type	Location	Sampling Dates	# of Samples	Sample Type	Analytical Method	Concentration (ppb) Range	Concentration (ppb) Mean	% Occurrence	Reference
	Pharmaceuticles	NS	1[c]	NS	GC/MS	237	NS	NS	Bursey and Pellizzari 1982
	Foundries	NS	1[c]	NS	GC/MS	136	NS	NS	Bursey and Pellizzari 1982
	Transportation Equip.	NS	2[c]	NS	GC/MS	28-318	173	NS	Bursey and Pellizzari 1982
	PTOWs[d]	NS	15[c]	NS	GC/MS	4.2-114	11.5	NS	Bursey and Pellizzari 1982
Urban Runoff									
	Washington, DC	NS-7/82	86	grab	NS	10	NS	4	Cole et al. 1984
Hazardous Waste Sites									
	Love Canal	8/80-10/80	NS	grab	GC/MS	NS[f]	NS	NS	Hauser and Bromberg 1982
	Valley of the Drums	1979	2[c]	grab	NS	15-37[g]	26	NS	Stonebraker and Smith 1980
	11 Disposal Sites	NS	8	grab/ composite	NS	29[h]	NS	12.5	Ghassemi et al. 1984
	Cooper Road site, NJ	NS	NS	NS	NS	NS[i]	NS	NS	VIEW database 1988
	Sheridan Disposal services, TX	NS	NS	NS	NS	2500[e]	NS	NS	VIEW database 1988
	Summit National site, OH	NS	NS	NS	NS	NS[g]	NS	NS	VIEW database 1988
	Unspecified site	NS	1	NS	NS	NS[g]	78	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	91	NS	CLSDB 1987
	Unspecified site	NS	2	NS	NS	NS[g]	315	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	1	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	360	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	538	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	48	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	12	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	20	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	48	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	157	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	11	NS	CLSDB 1987
	Unspecified site	NS	2	NS	NS	NS[g]	57.6	NS	CLSDB 1987

[a] Average of 8 samples
[b] µg in air per mL wastewater from purge and trap analysis
[c] number of positive samples
[d] Publicly owned treatment works
[e] detected in groundwater
ND not detected
NA not applicable
NS not specified
GC/MS gas chromatography/mass spectroscopy
GC/FID gas chromatography/flame ionization detector
[f] detected in sediment, soil, or water
[g] detected in water
[h] detected in leachate
[i] detected in groundwater

In general, isophorone is found in urban centers and appears to result from industrial activities. For example, its presence in the Delaware River near Philadelphia is the result of industrial effluents that are discharged into the sewer system (Hites 1979). The sewage is treated in Philadelphia's Northeast Sewage Treatment plant, which discharges its effluent into the Delaware River. Isophorone was detected in the Delaware River in the winter only; in the summer, biodegradation or other processes (e.g., sorption) may have removed it from the water column. Isophorone has been detected in the sediments of Lake Pontchartrain, which is located in the delta plain of the Mississippi River. Its presence probably is due to the many industries that are situated along the Mississippi River and use the river water as process water. Levels of isophorone in surface waters range from a trace to 100 ppb; however, this range represents only a few determinations.

The presence of isophorone in drinking water is probably the result of using contaminated surface water as a source of drinking water. Of the three cities for which drinking water data are listed, Philadelphia receives its drinking water from the Delaware River, Cincinnati from the Ohio River, and New Orleans from the Mississippi River. These rivers receive numerous industrial effluents.

As listed in Table 5-1, isophorone has been detected in the effluents of a variety of industries. Levels in industrial effluents range from 4.2-1380 ppb. Five reports of positive identifications were found in the open literature: a shale oil site; a tire manufacturing plant; sewer pump sample receiving wastes from phenolic resins manufacturing or processing, vinyl acetate, and polyvinylchloride process areas; final effluent from a sewage treatment system receiving wastes from plants producing plasticizers, butyl rubber, and olefin; and an unspecified effluent. The remaining samples listed in Table 5-1 are from an EPA data base of over 4000 analyses of organic pollutants in industrial wastewater made during the survey conducted in response to the consent decree between the Natural Resources Defense Council and EPA, June 7, 1976 (Bursey and Pellizzari 1982).

Isophorone also has been detected in urban runoff from Washington, DC (Cole et al. 1984). It has been detected in water (unspecified type) at 13 of 357 hazardous waste sites as shown in the contract laboratory statistical data base (1-538 ppb).

5.4.3 Soil

Isophorone has been identified in soil only at hazardous waste sites. The contract laboratory program statistical data base reports that isophorone has been detected at 1.68-6500 ppm in 4 of 357 hazardous waste sites.

5.4.4 Other Media

Isophorone has been detected in oysters (but not in clams) in Lake Pontchartrain, LA; the mean of eight samples of oysters from the Inner Harbor Navigation Canal section of the lake contained 38 ppb dry weight of isophorone. Hall et al. (1987) and De Vault (1985) did not detect isophorone in the fish in the Potomac River and Great Lakes Harbors and tributaries, respectively; in these cases, isophorone was not detected in the water either. Camanzo et al. (1987) reported finding isophorone in nearshore fish from 14 Lake Michigan tributaries and embayments; their results are presented in Table 5-2. Sampling was performed in 1983. Isophorone was detected in fish samples from all but 2 of the sites; the mean of the samples that had detectable levels of the compound was 1.17 mg/kg wet weight. In addition to isophorone, the authors also reported the lipid content of the composite fish samples. No correlation could be found between isophorone concentration and lipid content.

Johansson and Ryhage (1976) reported that isophorone was present in one of three samples of the pharmaceutical clofibrate [ethyl 2-(4-chlorophenoxy)-2-methylpropionate], which lowers elevated serum lipids. The analysis was performed on samples available from Sweden, but clofibrate is also available in the United States. The concentration of isophorone present in samples of the drug available in the United States was not reported.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

No ambient air monitoring data are available for isophorone; consequently, no potential inhalation exposures from ambient air can be estimated. Inhalation of isophorone from showering with contaminated water cannot be estimated from the available data (no measurements have been made).

Isophorone concentrations in surface waters and drinking waters are expected to vary considerably with season and with fluctuations in industrial discharges. Considering the dates of most of the positive identifications in surface and drinking water (middle to late 1970s), the effect of more stringent discharge limits in some industries since that time, and the probable seasonal, spatial, and temporal variations in concentrations, it is not possible to make an accurate estimate of ingestion intake of isophorone from drinking water without significant uncertainty. From the available data, it appears that long-term ingestion of isophorone from drinking water will be limited to those systems that receive their water from contaminated surface water sources and the seasonally averaged concentration in these waters probably will be <1 ppb.

Anjou and von Sydow (1967) reported that 0.2% of the essential oil of the American cranberry, *Vaccinium macrocarpon*, consisted of isophorone; they did not report the percentage of isophorone or the percentage of essential

TABLE 5-2. Detection of Isophorone in Fish near Lake Michigan

Location	Fish	Sampling Dates	# of Samples[a]	Mean Concentration[b]	% Lipid
St. Joseph River					
	Common Carp	1983	5	ND[c]	23.1
	Smallmouth Bass	1983	7	0.74	3.7
Kalamazoo River					
	Common Carp	1983	4	0.12	5.9
	Largemouth Bass	1983	4	0.72	3.1
Grand River					
	Common Carp	1983	3	ND	4.0
	Channel Catfish	1983	6	ND	13.5
Muskegon River					
	Common Carp	1983	4	0.94	17.9
	Pumpkinseed	1983	3	0.40	2.4
White Lake					
	Common Carp	1983	4	0.66	15.4
	Bowfin	1983	5	ND	12.1
Pere Marquette River					
	Common Carp	1983	6	3.13	11.0
	Bowfin	1983	8	ND	13.5
Manistee River					
	Common Carp	1983	4	ND	10.5
	Bowfin	1983	4	0.76	11.5
Platte River					
	Common Carp	1983	3	2.32	14.7
	Northern Pike	1983	6	ND	3.5
Boardman River					
	Smallmouth Bass	1983	6	3.61	5.4
	Rock Bass	1983	3	1.44	3.5
Grand Traverse Bay					
	Common Carp	1983	3	0.47	16.2
	Lake Trout	1983	4	2.33	18.8

TABLE 5-2 (continued)

Location	Fish	Sampling Dates	# of Samples[a]	Mean% Concentration	% Lipid
Manistique River					
	Smallmouth Bass	1983	5	1.03	4.5
	Northern Pike	1983	3	ND	2.1
Whitefish River					
	Common Carp	1983	11	0.88	16.4
	Rock Bass	1983	7	0.69	3.0
Escanaba River					
	Common Carp	1983	5	0.41	12.9
	Northern Pike	1983	6	0.48	2.9
Ford River					
	Northern Pike	1983	6	ND	3.0
	Rock Bass	1983	5	ND	3.1

[a] All samples are composites of the stated number of fish and were analyzed by gas chromatography/mass spectroscopy.
[b] mg/kg wet weight
[c] Not Detected
Source: Camanzo et al. 1987

oil in whole cranberries. Without this information it is not possible to estimate the concentration of isophorone in whole cranberries and compare the concentration to other sources. However, frequent consumption of cranberry containing products is unlikely to represent significant intake of isophorone. Ingestion of isophorone from consumption of fish and shellfish cannot validly be estimated from the available data (see Table 5-2).

Potential dermal exposure levels also are difficult to estimate from the available data. Dermal exposure from bathing in contaminated waters cannot be estimated without significant uncertainty. Other potential dermal exposures cannot be estimated with the available data.

Occupational exposures have been documented most frequently in the screen printing trade and are summarized in Table 5-3. During screen printing operations, both dermal and inhalation exposures can occur. Breathing zone concentrations during screen printing range from <1 to 25.7 ppm, while general area concentrations range from <1 to 16 ppm. The exposure level varies significantly with the ventilation present in the work area. While exposure estimate for a specific screen printing operation is possible, no reasonable estimates can be made for other operations that may use isophorone because of lack of data.

The relative contributions of the exposure routes and sources are as follows. For persons exposed to isophorone in the workplace, total doses will probably be substantially higher than those exposed only to ambient air and drinking water, and their inhalation and dermal exposures for the occupationally exposed can be assumed to result exclusively from the workplace exposures. Inhalation and dermal exposure for persons not exposed to isophorone in the workplace will most likely result from showering or bathing, but only in locations that receive their drinking water from contaminated surface water sources. These exposures are expected to be very small. In locations that do not have the potential for isophorone in the drinking water, any ingestion, inhalation, or dermal exposure is unlikely.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURE

Populations with potentially high exposure include those occupationally exposed to isophorone (e.g., screen print workers, some adhesives formulators and users, some coatings manufacturing and use workers). Individuals living near hazardous waste sites may be exposed to isophorone dermally, but probably not by inhalation. These individuals also may be exposed to isophorone by ingestion if they drink water from contaminated wells located down gradient from the site.

5.7 ADEQUACY OF THE DATABASE

Section 104 (i) (5) of CERCLA, 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

TABLE 5-3. Occupational Monitoring of Isophorone

Company	Process	Sample Type	Concentration (ppm) Range	Concentration (ppm) Mean[a]	Number of Samples	% Positive	Reference
Pre-Finish Metals	Wire Coating	Area	<1 - 3.37	1.13	24	33	NIOSH 1978a
Pre-Finish Metals	Wire Coating	Personal	<1 - 3.37	1.13	19	42	NIOSH 1978a
Joel and Aronoff	Screen Printing	Personal	<0.5 - 14	7.35	14	14	Lee and Fredrick 1981
Unspecified	Screen Printing	Area	3.5 - 16	10.2	46	100	Samimi 1982
Unspecified	Screen Printing	Personal	8.3 - 23	14.7	78	100	Samimi 1982
Electrocal	Screen Printing	Area	0.70 - 1.22	0.957	6	100	Bierbaum and Parnes 1974
Electrocal	Screen Printing	Personal	0.84 - 1.39	1.10	3	100	Bierbaum and Parnes 1974
Swinston Co.	Screen Printing	Personal	<0.47 - 25.7	12.9	7	29	Kominsky 1981
Garden City Engraving	Screen Printing	Area	<0.67 - 2.5	1.18	7	57	Salisbury 1983
Garden City Engraving	Screen Printing	Personal	<0.58 - 3.4	1.42	8	75	Salisbury 1983

[a] Mean of the positive samples

effects of isophorone is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

5.7.1 Data Needs

Physical and Chemical Properties. Physical and chemical properties are essential for estimating the partitioning of a chemical in the environment. Many physical and chemical properties are available for isophorone, but most do not have extensive experimental descriptions accompanying the data; therefore, an evaluation of the accuracy of the data is difficult. Specifically, measured vapor pressure, K_{oc}, and Henry's Law constant at environmentally significant temperatures would help to remove doubt regarding the accuracy of the estimated data. The data on physical properties form the basis of much of the input requirements for environmental models that predict the behavior of a chemical under specific conditions, including hazardous waste landfills. The data on the chemical properties, on the other hand, can be useful in predicting certain environmental fates of this chemical.

Environmental Fate. Sensitized photolysis studies in water and oxidation/reduction studies in both air and water are lacking, as are biodegradation studies in surface and groundwaters. These kinds of studies are important, since they represent the fundamental removal mechanisms available to isophorone in the environment. In addition, the kinetic studies for the atmospheric reactions are important for understanding the significance of a removal mechanism and predicting the reactions that may control the fate of a chemical in the environment.

Exposure Levels in Environmental Media. Environmental monitoring data are not available for soil and air, and the data available for water, sediments, and biota are not sufficient to determine ambient concentrations. These data would be helpful in determining the ambient concentrations of isophorone so that exposure estimates of the general population and the bioconcentration factor of this chemical in aquatic organisms can be made.

Exposure Levels in Humans. No information is available concerning exposure levels of isophorone in humans. A data base would be helpful in determining the current exposure levels, and thereby allowing an estimation of the average daily dose associated with various sources (e.g., living near a hazardous waste site; drinking water containing isophorone). A monitoring

program involving analyses of human tissues would be useful in assessing the magnitude of environmental exposures. Monitoring of human tissues from different locations and seasons and using different category of the population would be helpful so that the effects of such variables as occupational, geographical, and seasonal can be assessed.

Exposure Registries. An exposure registry (e.g., for occupationally exposed groups) currently is not available. The development of a registry of exposures would provide a useful reference tool in assessing exposure levels and frequencies. In addition, a registry developed on the basis of exposure sources would allow an assessment of the variations in exposure levels from one source to another and the effect of geographical, seasonal, regulatory actions on the level of exposure within a certain source. These assessments, in turn, would provide a better understanding of the needs for research or data acquisition based on the current exposure levels.

5.7.2 On-going Studies

No on-going studies were located in the available literature.

6. ANALYTICAL METHODS

6.1 BIOLOGICAL MATERIALS

No study was located regarding the analysis of isophorone in human biological materials, but animal studies (see Section 2.6) suggest that methods are available. In general, isophorone was extracted from the urine using ether (continuous extraction for 48 hours) followed by evaporation of the ether (Dutertre-Catella et al. 1978; Truhaut et al. 1970). The resulting residue was subjected to gas chromatography with flame ionization detector using the retention time as the indicator for the presence of isophorone or metabolites. In distribution studies, isophorone was extracted from minced tissues with dichloromethane, and the extract was analyzed by gas chromatography using the flame ionization detector (Dutertre-Catella 1976). In addition to these methods for analyzing isophorone in mammalian urine and tissues, Ozretich and Schroeder (1986) described a method for analyzing isophorone in fish tissue (Table 6-1).

6.2 ENVIRONMENTAL SAMPLES

Isophorone can be analyzed in municipal and industrial wastewater by EPA Test Method 609 - Nitroaromatics and Isophorone, or by EPA Test Method 625 Base/Neutrals and Acids (EPA 1982; Shafer 1982). These methods are adequate for measuring isophorone in most wastewaters, although interfering compounds may be present in some wastewaters. Method 609 involves the extraction of isophorone with methylene chloride followed by solvent exchange to hexane and analysis by gas chromatography (GC) using a flame ionization detector (FID). Method 625 is similar to Method 609, but the extraction is performed at pH 11 and is followed by concentration (without solvent exchange) and GC/MS analysis. The Contract Laboratory Procedure (EPA 1987a) is essentially identical (Table 6-1). The average recovery from reagent water and effluents was 49-67% for Method 609 and 75 ± 33% from reagent water for method 625. Method 609 shows a pronounced negative bias (the concentration detected by the method is lower than the true concentration present) (Kinzer et al. 1984). Table 6-1 presents accuracy and detection limit data for the methods. In air, isophorone can be analyzed by NIOSH Method 2508 (NIOSH 1984). The method involves drawing a 2 to 25 liter air sample through a petroleum based charcoal tube followed by carbon disulfide desorption and analysis by GC-FID. The method has a range of 0.2-10 mg per tube and a detection limit of 0.02 mg per tube. Table 6-1 presents accuracy information for this method.

The method for analyzing soil in the EPA Contract Laboratory Program involves the extraction of isophorone using methylene chloride followed by analysis by GC/MS. The usual detection limit is 330 ppb, although the exact detection limit is matrix dependent.

TABLE 6-1. Analytical Methods for Isophorone

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy[a]	Reference
Air	Charcoal tube collection and CS_2 desorption	GC-FID[b]	2 mg/m^3	104.9	NIOSH 1984
Water	Methylene chloride extraction, hexane solvent exchange, concentration	GC-FID	5.7 µg/L	49-67[c]	EPA 1982 Kinzer et al. 1984
	Methylene chloride extraction and concentration	GC/MS[d]	2.2 µg/L	75 ± 33[e]	EPA 1982 EPA 1987a (CLP)
Soil	Methylene chloride extraction and concentration	GC/MS	330 µg/kg	NS	EPA 1987a (CLP)
Fish Tissue	Macerate tissue mixed with anhydrous Na_2SO_4, extract with acetonitrile by sonocation. Concentrate extract, clean-up by column chromatography	GC/MS	NS	61	Ozretich and Schroeder 1986

[a] Average percent recovery
[b] Gas chromatography flame ionization detector
[c] Laboratory water and effluents
[d] Gas chromatography mass spectrometry
[e] Laboratory water
NS, not specified

6.3 ADEQUACY OF THE DATABASE

Section 104 (i) (5) of CERCLA, 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 isophorone is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

6.3.1 Data Needs

Methods for Parent Compound and Metabolites in Biological Materials. No information is available concerning the analysis of isophorone in biological materials. If information were available, it would allow both investigators and reviewers to assess the accuracy and uncertainty of the methods used. Furthermore, the ready availability of tested analytical methods would permit a standardized approach to the analysis of biological materials and allow a comparison of the levels of exposure with the possible health effects in humans.

Methods for Biomarkers of Exposure. No methods are available for the analysis of isophorone biomarkers of exposure in biological materials. If a method for the determination of the level of a specific biomarker were available in a biological medium, it could be used to indicate the level of exposure and the possible resultant health effect.

Methods for Parent Compound and Degradation Products in Environmental Media. Adequate methods appear to be available for the analysis of isophorone in groundwater, surface water, soil, and workplace air. No methods were found for the analysis of isophorone in ambient air, where concentrations are expected to be much lower than in workplace air. If the parent compound is stable as in the present case, it is essential that its concentrations in different environmental media be known so that the level of its exposure can be estimated.

No adequate methods appear to be available for the analysis of isophorone degradation products in environmental media. In cases where a degradation product of a chemical is toxic, it is important that its concentration in the environment be known. In certain instances, monitoring the level of a degradation product may be used as an indirect measurement of the parent compound in the environment.

6.3.2 On-going Studies

No studies were located regarding on-going analytical methods development for isophorone.

7. REGULATIONS AND ADVISORIES

International guidelines for isophorone were not located. National and state regulations and guidelines pertinent to human exposure to isophorone are summarized in Table 7-1.

Isophorone is regulated by the Clean Water Effluent Guidelines for the following industrial point sources: electroplating, steam electric, asbestos manufacturing, timber products processing, metal finishing, paving and roofing, paint formulating, ink formulating, gum and wood, carbon black, aluminum forming, and electrical and electronic components (EPA 1988a).

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Isophorone

Agency	Description	Value	Reference
		National	
Regulations			
a. Air			
OSHA	Permissible Exposure Limit	4 ppm	OSHA 1989 29 CFR 1910.1000
b. Water			
EPA OWRS	Ambient Water Quality Criterion	5.2 mg/L	EPA 1980b 45 FR 79318 (11/28/80)
c. Non-specific Media			
EPA OERR	Reportable Quantity	5000 lb	EPA 1985b 50 FR 13456 (4/4/85) 40 CFR 117 and 302
Guidelines			
a. Air			
ACGIH	Ceiling Limit for Occupational Exposure	5 ppm	ACGIH 1988
NIOSH	Recommended Exposure Limit for Occupational Exposure as a TWA for up to 10-hour workshift	4 ppm	NIOSH 1978b
b. Other			
EPA	Reference Dose for Chronic Oral Exposure	0.15 mg/kg/day	EPA 1988b
EPA	q1* for Oral exposure (proposed)	$4x10^{-3}$ $(mg/kg/day)^{-1}$	EPA 1986,1987b
EPA	Cancer Classification (proposed)	Group C[a]	EPA 1987b

TABLE 7-1 (continued)

Agency	Description	Value	References
		State	
State agencies	Drinking water quality guidelines		FSTRAC 1988
	Kansas	5200 μg/L	
State	Acceptable ambient air concentrations		NATICH 1987
	Connecticut	460 $\mu g/m^3$ (8 hr avg)	
	Nevada	0.595 mg/m^3 (8 hr avg)	
	New York	83.3 $\mu g/m^3$ (annual avg)	
	Virginia	200 $\mu g/m^3$ (24 hr avg)	
	Acceptable Ambient Limit		
	Kentucky	2.5 mg/m^3	State of Kentucky 1986

[a] Possible Human Carcinogen

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9. GLOSSARY

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

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

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

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

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

Carcinogen -- A chemical capable of inducing cancer.

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

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

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

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

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

9. GLOSSARY

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

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

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

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

In vivo -- Occurring within the living organism.

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

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

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

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

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

LT_{50} (lethal time) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

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

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

9. GLOSSARY

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

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

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

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

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

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

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

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

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

9. GLOSSARY

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

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

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

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

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

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

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

APPENDIX: PEER REVIEW

A peer review panel was assembled for isophorone. The panel consisted of the following members: Dr. Rip G. Rice, Private Consultant, Rice Incorporated, Ashton, MD; Dr. Anthony P. DeCaprio, Private Consultant, Albany, NY; Dr. Bhola N. Banerjee, Private Consultant, Potomac, MD; and Dr. Judith S. Bellin, Private Consultant, Washington, DC These experts collectively have knowledge of isophorone's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in the Superfund Amendments and Reauthorization Act of 1986, Section 110.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.

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