TOXICOLOGICAL PROFILE FOR ACETONE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles contact ATSDR at:

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The revised list of the 275 most hazardous substances was published in the Federal Register on October 28, 1992 (57 FR 48801). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); and October 17, 1991 (56 FR 52166).

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

(A) The examination, summary, and interpretation of available toxicological information and epidemiological evaluations on a 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 that present a significant risk to human health of acute, subacute, and chronic health effects.

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

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

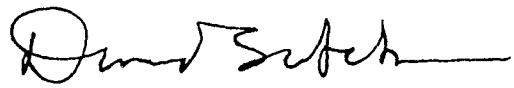
The ATSDR toxicological profile is intended to succinctly characterize the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological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

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

Foreword

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

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. 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.



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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying endpoints.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

PEER REVIEW

A peer review panel was assembled for acetone. The panel consisted of the following members:

1 . Dr. Elizabeth Jeffery, Associate Professor of Toxicology, University of Illinois, Urbana, Illinois

2 . Dr. Peter G. Lacouture, Associate Director, Clinical Research, Purdue Frederick Company, Norwalk, Connecticut

3 . Dr. John Morris, Associate Professor of Pharmacology and Toxicology, Toxicology Program, School of Pharmacy, University of Connecticut, Storrs, Connecticut.

These experts collectively have knowledge of acetone'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 Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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

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

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about acetone and the effects of exposure. This information is important because this chemical may harm you.

The Environmental Protection Agency (EPA) has identified 1,350 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are targeted for long-term federal clean-up. Acetone has been found in at least 560 NPL sites. However, it's unknown how many NPL sites have been evaluated for this substance.

As EPA tests more sites, the sites with acetone may increase. This is important because exposure to acetone may harm you and because these sites are or may be sources of exposure.

When a large industrial plant or a small container releases a substance, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it by breathing, eating, touching, or drinking.

If you are exposed to acetone, many factors determine if you'll be harmed and how badly. These factors include the dose (how much), the duration (how long), and how you're exposed. You must also consider the other chemicals you're exposed to and your age, sex, nutritional status, family traits, lifestyle, and state of health.

1.1 WHAT IS ACETONE?

Acetone is a chemical that is found naturally in the environment and is also produced by industries. Low levels of acetone are normally present in the body from the breakdown of fat; the body can use it in normal processes that make sugar and fat (see Section 1.4). Acetone is a colorless liquid with a distinct smell and taste. People begin to smell acetone in air at 100 to 140 parts of acetone in a million parts of air (ppm), though some can smell it at much lower levels. Most people begin to detect the presence of acetone in water at 20 ppm. Acetone evaporates readily into the air and mixes well with water. Most acetone produced is

used to make other chemicals that make plastics, fibers, and drugs. Acetone is also used to dissolve other substances. You will find further information on the physical and chemical properties of acetone, and its production and use in Chapters 3 and 4.

1.2 WHAT HAPPENS TO ACETONE WHEN IT ENTERS THE ENVIRONMENT?

Acetone enters the air, water, and soil as a result of natural processes and human activities. Acetone occurs naturally in plants, trees, volcanic gases, and forest fires. People and animals breathe out acetone produced from the natural breakdown of body fat. Acetone is also released during its manufacture and use, in exhaust from automobiles, and from tobacco smoke, landfills, and certain kinds of burning waste materials. The levels of acetone in soil increase mainly because of acetone-containing wastes being buried in landfills. Acetone is present as a gas in air. Some acetone in air is lost when it reacts with sunlight and other chemicals. Rain and snow also remove small amounts of acetone from the atmosphere and, in the process, deposit it on land and water. About half the acetone in a typical atmosphere at any time will be lost in 22 days. Microbes (minute life forms) in water remove some acetone from water. Some acetone in water will evaporate into air. About half the acetone in a stream will be removed from water in less than a day. Fish do not store acetone from water in their bodies. Microbes in soil remove part of the acetone in soil. Some is lost from soil by evaporation. Acetone molecules do not bind tightly to soil. Rainwater and melted snow dissolve acetone and carry it deeper into the soil to groundwater. You will find further information about the fate and movement of acetone in the environment in Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO ACETONE?

Your body makes small amounts of acetone. You can be exposed to a small amount of acetone by breathing air, drinking water, and eating food with acetone. You can also be exposed by contact with household chemicals with acetone. Several consumer products, including certain nail polish removers, particle board, some paint removers, many liquid or paste waxes or polishes, and certain detergents or cleansers, contain acetone. You can also be exposed to acetone if you are exposed to isopropyl alcohol, because isopropyl alcohol changes

to acetone in the body. The level of acetone in air and water is generally low. The amount of acetone in the air of cities is generally higher than in remote and rural areas. The typical level of acetone in the air of cities in the United States is about 7 parts of acetone per billion parts of air (ppb). The level of acetone in air inside homes is usually slightly higher than in outside air (8 ppb versus 7 ppb). This is because of household chemical use inside homes. Acetone in drinking water is so low that its levels have not been measured in many samples. In a national survey, the acetone level in drinking water from Seattle, Washington, was 1 ppb. Acetone occurs naturally in many fruits and vegetables. The amount of acetone in food does not increase because of processing or packaging. The average amount of acetone an adult in the United States gets from food is not known.

People who work in certain industries that process and use acetone can be exposed to higher levels than the general populace. These industries include certain paint, plastic, artificial fiber, and shoe factories. Professional painters and commercial and household cleaners are also likely to breathe or touch higher acetone concentrations than the general population. As a member of the general public, you may be exposed to higher than normal levels of acetone if you smoke cigarettes, frequently use acetone nail polish removers, live near landfill sites that contain acetone, live near busy roadways (because automobile exhaust contains acetone), or live near other facilities that are known to release acetone, such as incinerators. The exposure from these sources will be mainly from breathing air that contains acetone or by direct skin contact with it. In addition, children can be exposed to acetone by eating dirt or by placing dirty hands in their mouths after exposing their skin to dirt from landfill sites. You will find further information about acetone exposure in Chapter 5.

1.4 HOW CAN ACETONE ENTER AND LEAVE MY BODY?

Your body normally contains some acetone because it’s made during the breakdown of fat. Your body will make more acetone from body fat if you are on a low-fat diet. In addition to the acetone that your body makes from normal processes, acetone can enter your body if you breathe air that contains acetone, drink water or eat food that contains acetone, or if you touch liquid acetone or soil that contains acetone.

The bloodstream absorbs acetone rapidly and completely from the lungs and stomach. The bloodstream can also absorb acetone from the skin, but less rapidly than from the lungs and stomach. Blood carries acetone to all body organs, but it does not stay there very long.

The liver breaks down acetone to chemicals that are not harmful. The body uses these chemical to make glucose (sugar) and fats that make energy for normal body functions. The breakdown of sugar for energy makes carbon dioxide that leaves your body in the air you breathe out. These are normal processes in the body.

Not all the acetone that enters your body from outside sources is broken down. The amount that is not broken down leaves your body mostly in the air that you breathe out. You also breathe out more carbon dioxide than normal if you are exposed to acetone from sources outside the body because more carbon dioxide is made from the extra acetone.

Only a small amount of acetone that is not broken down leaves the body in the urine. The acetone that is not used to make sugar leaves your body within a few days in the air you breathe out and in the urine. The amount of acetone that enters and leaves your body depends on how much you're exposed to and for how long. The higher the level of acetone and the longer that you are exposed will cause acetone to leave your body more slowly, but almost all the acetone will leave your body within 3 days after your exposure stops. If you exercise or work while exposed to acetone in air, more will enter your lungs because you breathe faster and more deeply during exercise. For more information on how acetone enters and leaves the body, see Chapter 2.

1.5 HOW CAN ACETONE AFFECT MY HEALTH?

As mentioned in Section 1.4, low levels of acetone are normally present in the body from the breakdown of fat. The body uses acetone in normal processes that make sugar and fats that make energy for normal body functions. Many conditions can lead to higher-than-average amounts of acetone in the body. For example, babies, pregnant women, diabetics, and people who exercise, diet, have physical trauma, or drink alcohol can have higher amounts of acetone

in their bodies. These higher amounts of acetone usually don't cause health problems. In addition, acetone can prevent convulsions.

Most of the information on how acetone affects human health comes from medical exams of workers on a single workday; from lab experiments in humans exposed to acetone in air for a few days; and from cases of people who swallowed acetone-based glue or fingernail polish remover.

Workers and people exposed to acetone in the lab complained that acetone irritated their noses, throats, lungs, and eyes. Some people feel this irritation at levels of 100 ppm acetone in the air, and more people feel the irritation as the level in air increases. The workers who complained of irritation were exposed to levels of 900 ppm or more. Workers exposed to acetone at 12,000 ppm or higher also complained of headache, lightheadedness, dizziness, unsteadiness, and confusion depending on how long they were exposed (from 2 minutes to 4 hours). Two workers exposed for 4 hours became unconscious.

In addition, some people who had casts applied with acetone were exposed to acetone that evaporated into air during and after the casts were applied. These patients became nauseous, vomited blood, and became unconscious. These cases happened many years ago; modern hospitals have different methods that don't use acetone when casts are applied. Some people exposed to acetone in the air at about 250 ppm for several hours in the lab had headaches and lacked energy, and they also had some mild behavioral effects. These effects showed up in tests of how long it takes to react to a visual stimulus or the ability to hear different sounds. Some people exposed to 500 ppm in the air for several hours in the lab had effects on the blood, but other studies showed no effects on the blood at even higher exposure levels.

Some women exposed to 1,000 ppm for about 8 hours in a lab said that their periods came earlier than expected. Workers are not usually exposed to levels higher than 750 ppm anymore because of current government regulations. The regulation says workroom air should contain no more than an average of 750 ppm. Most people can smell acetone in the air at 100 to 140 ppm; that means you will probably smell acetone before you feel effects like

headache and confusion. Levels of acetone in air in rural areas and in cities (less than 8 ppb) are generally lower than this.

People who swallowed acetone or substances that contained acetone became unconscious, but they recovered in the hospital. The amount of acetone that these people swallowed was not always known, but one man swallowed about 2,250 milligrams of pure acetone per kilogram of body weight (2,250 mg/kg). In addition to becoming unconscious, he had tissue damage in his mouth and he later developed a limp, which eventually cleared up, and symptoms similar to diabetes (excessive thirst, frequent urination). The amount of acetone in water or food would never be high enough to cause these effects, but people, especially children, could accidentally swallow enough acetone in nail polish remover or some household cleaners to cause such effects.

In a lab experiment, people who had liquid acetone applied directly on their skin and held there for a half hour developed skin irritation. When the skin was looked at under a microscope, some of the skin cells were damaged.

Animals briefly exposed to high levels of acetone in the air also had lung irritation and became unconscious; some died. Exposure at lower levels for short periods also affected their behavior. Pregnant animals that were exposed to high levels of acetone in air had livers that weighed more than usual and had fewer fetuses. The fetuses weighed less than normal and had delayed bone development. We do not know how exposure to acetone in air for longer than 2 weeks affects animals.

Animals given large amounts of acetone to swallow or drink for short periods had bone marrow hypoplasia (fewer new cells being made), degeneration of kidneys, heavier than normal livers and bigger liver cells, and collapse and listlessness. Pregnant mice that swallowed acetone had lower body weights and produced fewer newborn mice. More of the newborns of mice that had swallowed acetone died than newborns of mice that were not given acetone.

Male rats that swallowed or drank even small amounts of acetone for long periods had anemia and kidney disease. The female rats did not have anemia, but they had kidney disease when they swallowed a much larger amount of acetone than the male rats swallowed. The female rats had livers and kidneys that weighed more than normal, and so did the male rats, but only when they swallowed larger amounts of acetone than the females swallowed. The male rats also had abnormal sperm. The female rats did not have any effects in their reproductive organs. Rats also had signs that acetone caused effects on their nervous systems.

Acetone is irritating to the skin of animals when it is placed directly on their skin, and it burns their eyes when placed directly in their eyes. One kind of animal (guinea pigs) even developed cataracts in their eyes when acetone was placed on their skin.

We do not know whether many of the effects seen in animals would occur in humans. People exposed to acetone were not examined for some effects or could not be examined for effects that can be seen only by looking at internal organs under a microscope. The findings in animals show that male rats are more likely than female rats to get blood and kidney disease and effects on reproductive organs after exposure to acetone. This suggests that men might be more likely to have effects of exposure to acetone than women.

One effect of acetone seen in animals is an increase in the amount of certain enzymes (chemicals in the body that help break down natural substances in the body and chemicals that enter the body). The increase in these enzymes caused by acetone exposure can make some chemicals more harmful. This is one reason that people should be concerned about being exposed to acetone; exposure is very likely to mixtures of chemicals in the environment, near hazardous waste sites, or in the workplace is very likely.

Acetone does not cause skin cancer in animals when it is applied to their skin. We don’t know whether acetone would cause cancer after breathing or swallowing it for long periods, because no tests have been done. The Department of Health and Human Services and the International Agency for Research on Cancer have not classified acetone for carcinogenic

effects. The EPA has determined that acetone is not classifiable as to its human carcinogenicity.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ACETONE?

Acetone can be measured in the air you breathe out, in the blood, and in the urine. Methods for measuring acetone in breath, blood, and urine are available at most modern testing labs. Doctors' offices may not have the necessary equipment, but your doctor can take blood and urine samples and send them to a testing lab. The measurement of acetone in breath, blood, and urine can determine whether you have been exposed to acetone if the levels are higher than those normally seen. They can even predict how much acetone you were exposed to. However, normal levels of acetone in breath, blood, and urine can vary widely depending on many factors, such as infancy, pregnancy, lactation, diabetes, physical exercise, dieting, physical trauma, and alcohol. The odor of acetone on your breath can alert a doctor that you have been exposed to acetone. An odor of acetone on your breath could also mean that you have diabetes. Because acetone leaves your body within a few days after exposure, these tests can tell only that you have been exposed to acetone within the last 2 or 3 days. These tests cannot tell whether you will experience any health effects related to your exposure.

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

EPA requires that spills of 5,000 pounds or more of acetone be reported. To protect workers, the Occupational Safety and Health Administration (OSHA) has set a legal limit of 750 ppm of acetone in workroom air. The regulation means that the workroom air should contain no more than an average of 750 ppm of acetone over an 8-hour working shift or over a 40-hour workweek.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333
404-639-6000

This agency can also tell you the location of occupational and environmental health clinics. These clinics specialize in the recognition evaluation, and treatment of illness resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of acetone. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure - inhalation, oral, and dermal; and then by health effect - death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods - acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest- observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAEL have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify

these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for acetone. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

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

A User’s Guide has been provided at the end of this profile (see Appendix A). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

2.2.1.1 Death

In a retrospective mortality study of 948 employees (697 men, 251 women) of a cellulose fiber plant where acetone was used as the only solvent, no significant excess risk of death from any cause (all causes, malignant neoplasm, circulatory system disease, ischemic heart disease) compared with rates for the U.S. general population was found (Ott et al. 1983a, 1983b). The workers had been employed at the plant for at least 3 months to 23 years. Industrial hygiene surveys found that median time-weighted-average acetone concentrations were 380, 770, and 1,070 ppm based on job categories.

As shown in Table 2-l and Figure 2-1, high concentrations of acetone were required to produce death in animals. An 8-hour LC_{50} value of 21,091 ppm and a 4-hour LC_{50} value of 31,994 ppm were found for female rats (Pozzani et al. 1959). Inhalation exposure to acetone for a few hours has resulted in death in rats at concentrations ranging from 16, inhalation exposure to acetone for a few hours has resulted in death in rats at concentrations ranging from 16,000 to 50,600 ppm (Bruckner and Peterson 1981a; Smyth et al. 1962) and in guinea pigs from 10,000 to 50,000 ppm (Specht et al. 1939). In general, higher concentrations of acetone resulted in death sooner than lower concentrations. That very high concentrations of acetone are required to cause death of animals is reinforced by the fact that no deaths were reported for rats exposed to acetone at 4,210 for 8 hours to 126-129 ppm for 25 minutes (Haggard et al. 1944) or mice exposed to $\leq$84,194 ppm for 8 hours (Mashbitz et al. 1936). No studies were located regarding death of animals after intermediate- or chronic-duration inhalation exposure to acetone.

2.2.1.2 Systemic Effects

The systemic effects of inhalation exposure to acetone in humans and animals are discussed below. The highest NOAEL values and all LOAEL values for each systemic effect from each reliable study are recorded in Table 2-l and plotted in Figure 2-l.

Respiratory Effects. The only effect on the respiratory system observed in humans exposed to acetone vapors is irritation of the nose, throat, trachea, and lungs. The irritating properties of acetone in humans have been noted both in workers who were exposed to acetone occupationally (Raleigh and

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

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	1 d 4 hr/d				16000 (1/6 died)	Smyth et al. 1968
2	Rat	4 or 8 hr				21091 (LC_{50}-8 hr) 31994 (LC_{50}-4 hr)	Pozzani et al. 1959
3	Rat	1 d 3 hr/d				50600 (5/5 died)	Bruckner and Peterson 1981a
4	Gn pig	1 d 3-4 hr/d				50000 (8/8 died)	Specht et al. 1939
5	Gn pig	2 d 24 hr/d				10000 (5/5 died)	Specht et al. 1939
6	Gn pig	1 d 22-26 hr/d				20000 (8/9 died)	Specht et al. 1939
7	Gn pig	1 d 25 min-23.4 hr/d				21800 (2/10 died)	Specht et al. 1939
Systemic							
8	Human	6 d 6 hr/d	Resp		250 (irritation of nose and throat)		Matsushita et al. 1969a
			Hemato	250	500 (increased white blood cell count; decreased phagocytic activity of neutrophils)		
9	Human	1 d 3-5 min/d	Resp	200	500 (nose and throat irritation)		Nelson et al. 1943
10	Human	2-3 d 8 hr/d	Resp		901 (throat and nose irritation)		Raleigh and McGee 1972

TABLE 2-1. Levels of Significant Exposure to Acetone - Inhalation *(continued)*

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
11	Human	1 d 6 hr/d	Resp		100 (irritation of nose, throat and trachea)		Matsushita et al. 1969b
			Hemato	250	500 (increased white blood cell count; decreased phagocytic activity of neutrophils)		
12	Human	1 d 2 hr/d	Hemato Hepatic Renal	500 500 500			DiVincenzo et al. 1973
13	Human	1 d 2 min- 4 hr/d	Resp		12000 (throat and lung irritation)		Ross 1973
14	Human	7 d 8 hr/d	Resp		1006 (irritation of nose and throat)		Raleigh and McGee 1972
15	Rat	14 d 7 d/wk 6 hr/d Gd 6-19	Other	2200	11000 (significantly reduced body weight [7%], uterine weight [19%] and extra-gestational weight gain [36%] of dams)		NTP 1988
16	Rat	2 wk 5 d/wk 4 hr/d	Other (body weight)	16000			Goldberg et al. 1964
17	Gn pig	1 d 3-8.75 hr/d	Resp			50000 (pulomonary congestion and hemorrhage)	Specht et al. 1939
			Hepatic		50000 (mild fatty deposition)		
			Renal			50000 (congestion and distention of glomeruli)	
			Other			50000 (congestion and hemorrhage of spleen)	

TABLE 2-1. Levels of Significant Exposure to Acetone - Inhalation *(continued)*

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
18	Gn pig	1 d 22-26 hr/d	Resp			20000 (marked congestion and hemorrhage of lungs)	Specht et al. 1939
			Hepatic			20000 (fatty liver in guinea pigs that died)	
			Renal			20000 (distention of glomerular capsule)	
			Other			20000 (marked congestion and hemorrhage of spleen)	
19	Gn pig	2 d 24 hr/d	Resp			10000 (lung congestion in guinea pigs that died)	Specht et al. 1939
			Hepatic			10000 (fatty liver in guinea pigs that died)	
			Renal			10000 (renal tubular distention)	
			Other			10000 (congestion of spleen)	
20	Mouse	1 or 5 d 0.5 hr/d	Resp	6000			Schaper and Brost 1991
21	Mouse	1 d 10 min/d	Resp		77516 (RC_{50} for sensory irritation)		Kane et al. 1980
22	Mouse	12 d 7 d/wk 6 hr/d Gd 6-17	Hepatic	2200	6600 (significantly increased absolute and relative liver weight of dams)		NTP 1988
			Other (body weight)	6600			

TABLE 2-1. Levels of Significant Exposure to Acetone - Inhalation *(continued)*

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
Immunological							
23	Human	6 d 6 hr/d		250	500 (increased white blood cell count; decreased phagocytic activity of neutrophils)		Matsushita et al. 1969a
24	Human	1 d 6 hr/d		250	500 (increased white blood cell count; decreased phagocytic activity of neutrophils)		Matsushita et al. 1969b
Neurological							
25	Human	2-3 d 8 hr/d		901			Raleigh and McGee 1972
26	Human	7 d 8 hr/d			1006 (headache, light-headedness)		Raleigh and McGee 1972
27	Human	1 d 2 min-4 hr/d				12000 (unconsciousness, dizziness, unsteadiness, confusion, headache)	Ross 1973
28	Human	1-8 hr				21049 (signs of narcosis in 3-6 hours, loss of righting reflex in 8 hours)	Haggard et al. 1944
29	Human	1 d 6 hr/d			250 (lack of energy, general weakness)		Matsushita et al. 1969b
30	Human	1 d 4 hr/d			237[b] (increases in response and % false negatives in auditory discrimination; increased anger, hostility)		Dick et al. 1989

TABLE 2-1. Levels of Significant Exposure to Acetone - Inhalation *(continued)*

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
31	Human	6 d 6 hr/d			250 (delayed visual reaction time, headache, lack of energy, weakness)		Matsushita et al. 1969a
32	Human	4-8 hr			1000 (subjective symptoms of tension, tiredness, complaints and annoyance, not otherwise specified)		Seeber et al. 1992
33	Rat	1 d 3 hr/d				12600 (CNS depression measured by unconditioned performance and reflex tests)	Bruckner and Peterson 1981a
34	Rat	2 wk 5 d/wk 4 hr/d		3000		6000 (inhibition of avoidance behavior in 38% of the rats)	Goldberg et al. 1964
35	Rat	5 min- 8 hr		4210		10524 (signs of narcosis-loss of coordination in 100-250 minutes)	Haggard et al. 1944
36	Gn pig	1 d 25 min- 23.4 hr/d				21800 (narcosis, coma, paralysis)	Specht et al. 1939

TABLE 2-1. Levels of Significant Exposure to Acetone - Inhalation *(continued)*

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
37	Mouse	1 d		1000		3000 (10% decreased response to food presentation in a fixed interval operant behavioral test)	Glowa and Dews 1987
38	Mouse	4 hr		2032		2580 (39% decrease in duration of immobility in behavioral despair swimming test p<0.05)	DeCeaurriz et al. 1984
39	Mouse	1 d 6 hr/d				11000 (severe narcosis)	NTP 1988
40	Mouse	4 hr				16839 (drowsiness, staggering, prostration, clonic movements of hind legs, and deep narcosis)	Mashbitz et al. 1936
Developmental							
41	Rat	14 d 7 d/wk 6 hr/d Gd 6-19		2200	11000 (decreased fetal weight)		NTP 1988
42	Mouse	12 d 7 d/wk 6 hr/d Gd 6-17		2200		6600 (significantly increased incidence of late resorption, decreased fetal weight, reduced sternabral ossification)	NTP 1988
Reproductive							
43	Human	1 d 7.5 hr/d			1000 (shortened menstrual cycle)		Stewart et al. 1975

TABLE 2-1. Levels of Significant Exposure to Acetone - Inhalation *(continued)*

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
44	Rat	14 d 7 d/wk 6 hr/d Gd 6-19		11000			NTP 1988
45	Mouse	12 d 7 d/wk 6 hr/d Gd 6-17		6600			NTP 1988
INTERMEDIATE EXPOSURE							
Systemic							
46	Human	6 wk 2-5 d/wk 1-7.5 hr/d	Resp Cardio Hemato Hepatic Renal	1250 1250 1250 1250 1250			Stewart et al. 1975
47	Rat	2-8 wk 5 d/wk 3 hr/d	Resp Cardio Hepatic Renal	19000 19000 19000 19000			Bruckner and Peterson 1981b
Neurological							
48	Human	6 wk 2-5 d/wk 1-7.5 hr/d			1250[c] (increased visual evoked response)		Stewart et al. 1975
49	Rat	2-8 wk 5 d/wk 3 hr/d		19000			Bruckner and Peterson 1981b

TABLE 2-1. Levels of Significant Exposure to Acetone - Inhalation *(continued)*

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
CHRONIC EXPOSURE							
Systemic							
50	Human	3 mo-23 yr 5 d/wk 8 hr/d (occup)	Hemato Hepatic	1070 1070			Ott et al. 1983a; 1983c

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive an acute inhalation minimal risk level (MRL) of 26 ppm; concentration divided by an uncertainty factor of 9 (3 for use of a minimal LOAEL and 3 for human variability)
[c]Used to derive intermediate and chronic inhalation MRLs of 13 ppm; concentration divided by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability)

Cardio = cardiovascular; CNS = central nervous system; d = day(s); Gd = gestation day(s); Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; min = minute(s); NOAEL = no-observed-adverse-effect level; occup = occupational; RC_{50} = the concentration necessary to detect a 50% decrease in respiratory rate; Resp = respiratory; wk = week(s); yr = year(s)

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

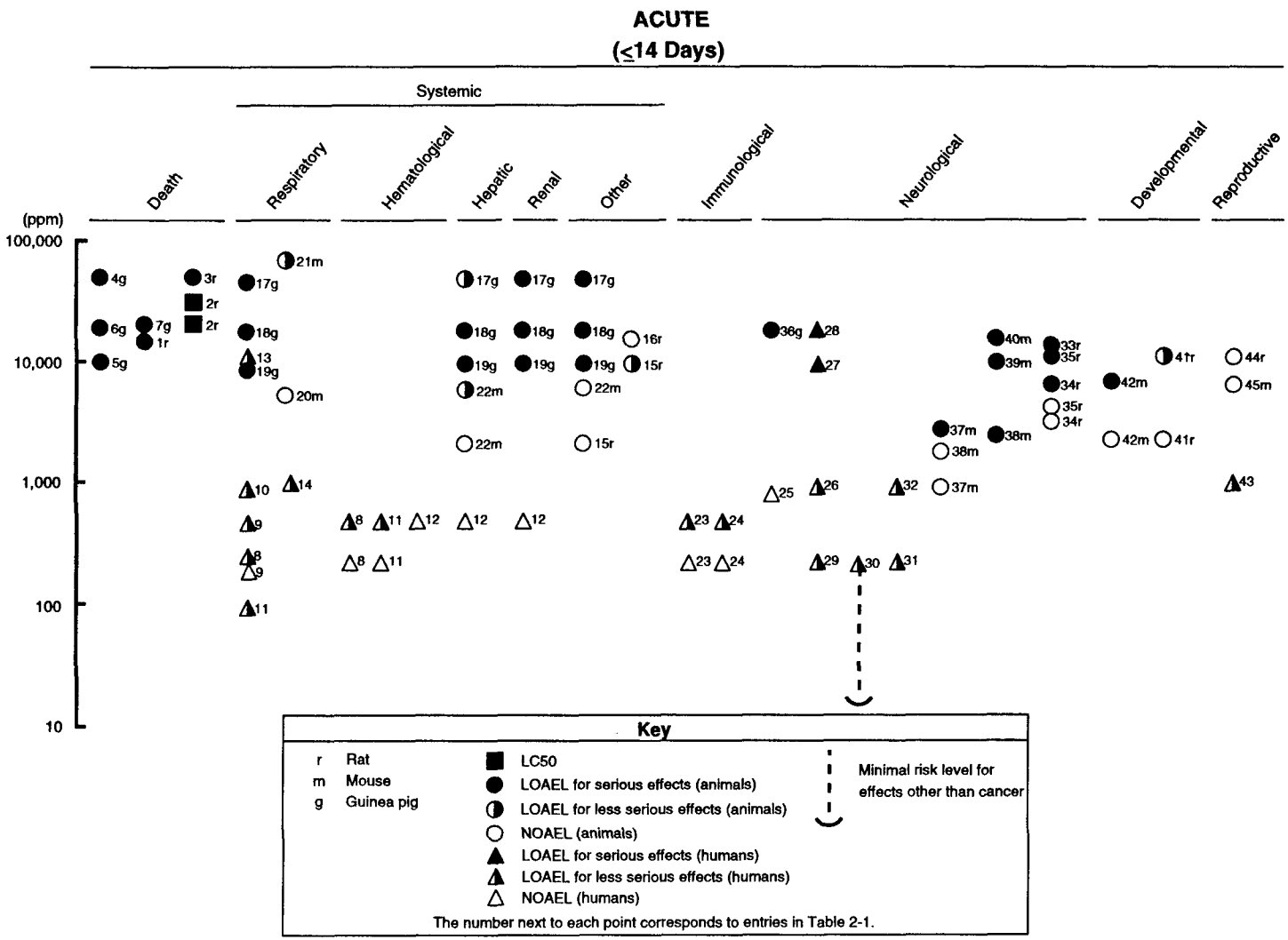
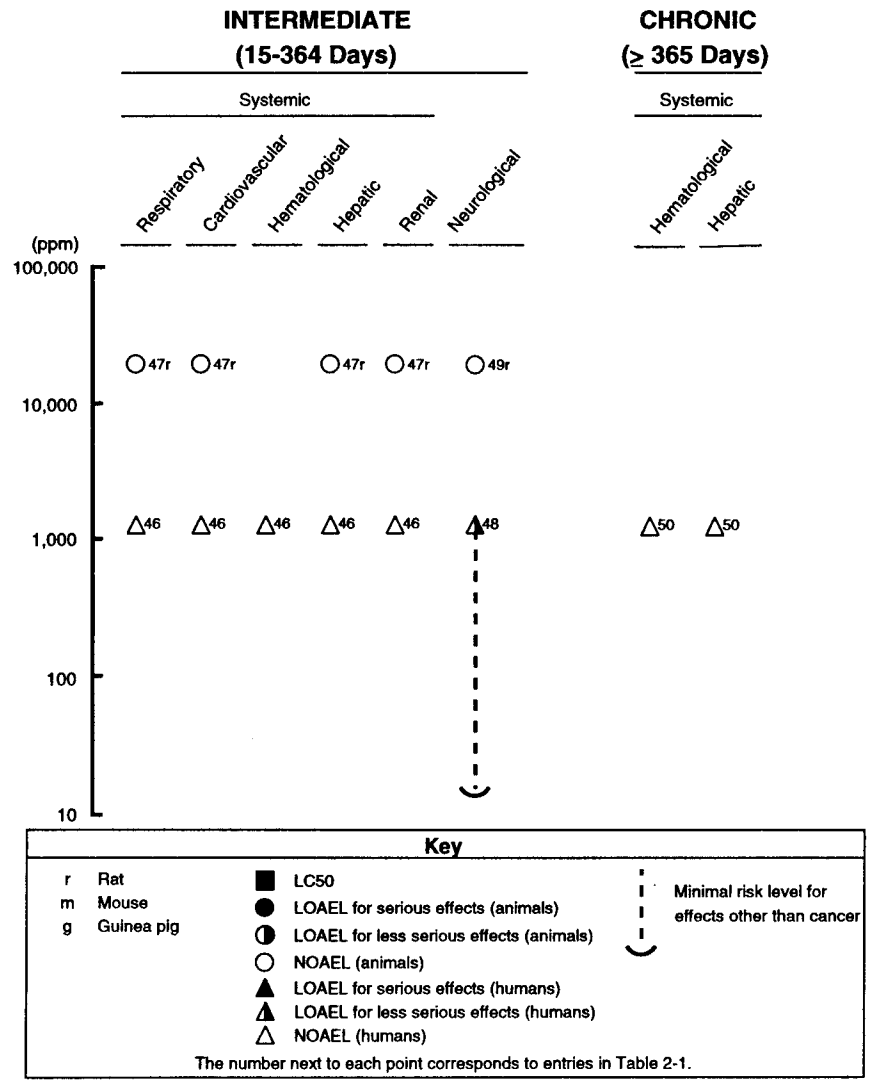


FIGURE 2-1. Levels of Significant Exposure to Acetone - Inhalation *(continued)*



McGee 1972; Ross 1973) and in volunteers under controlled laboratory conditions (Matsushita et al. 1969a, 1969b; Nelson et al. 1943). Complaints of irritation were reported by workers with average exposures to acetone in the workroom of ≥901 ppm (Raleigh and McGee 1972; Ross 1973). In controlled situations, the volunteers had been asked to give their subjective complaints, and some of the volunteers reported that exposure to 100 ppm for 6 hours was irritating, with more subjects reporting irritation at increasing exposure levels (Matsushita et al. 1969b). Subjective symptoms also included the loss of the ability to smell acetone as exposure proceeded. In another controlled experiment, the majority of subjects, although exposed for only 3-5 minutes, estimated that they could tolerate an exposure level of 200 ppm for an 8-hour workshift (Nelson et al. 1943). Pulmonary function testing of volunteers exposed <1,250 ppm acetone intermittently for various durations in a complex protocol revealed no abnormalities caused by the exposure (Stewart et al. 1975). The volunteers did experience throat irritation sporadically.

Exposure of animals to much higher concentrations of acetone than those reported in humans has resulted in respiratory effects. Pulmonary congestion, edema, and hemorrhage of the lungs were observed in guinea pigs that died after exposure to 10,000 ppm continuously for 1 or 2 days, to 20,000 ppm continuously for 1 day, or to 50,000 ppm for a few hours (Specht et al. 1939). The congestion and edema were attributed to the irritating effects of acetone on the mucosa. The hemorrhage may have been a consequence of death. Respiratory rates also decreased in the guinea pigs during exposures, but the decrease was probably a consequence of the narcotic effects of acetone (see Section 2.2.1.4). In mice exposed to acetone for 10 minutes, the calculated concentration of acetone that decreased the respiratory rate 50% (RC_{50}) was 77,516 ppm (Kane et al. 1980). The decrease in respiratory rate was considered to be due to sensory irritation, but adaptation to the irritant properties developed. The RC_{50} for acetone was higher than the values calculated for other solvents, indicating that acetone is a weak irritant. In mice exposed to 6,000 ppm acetone for 0.5 hours/day for 1 or 5 days, no effects on the time of inspiration, time of expiration, time between breaths, or tidal volume were found (Schaper and Brost 1991). In addition, acetone exposure caused no changes in lung weight, lung volume displacement, or histological evidence of pulmonary pathology.

Histological examination of the lungs of rats exposed intermittently to a high concentration of acetone (19,000 ppm) for 2-8 weeks revealed no evidence of treatment-related lesions (Bruckner and Peterson 1981b).

Cardiovascular Effects. Information regarding cardiovascular effects in humans following inhalation exposure to acetone is limited. High pulse rates (120-160/minute) were commonly found in patients exposed to acetone by inhalation and/or dermally after application of casts for which acetone was used in the setting solution (Chatterton and Elliott 1946; Hift and Pate1 1961; Pomerantz 1950; Renshaw and Mitchell 1956). In a controlled laboratory study using a complex protocol, electrocardiography of volunteers exposed to $\leq$1,250 ppm acetone intermittently for various durations revealed no alterations, compared with their preexposure electrocardiograms (Stewart et al. 1975). A retrospective mortality study of 948 workers (697 men, 251 women) employed for at least 3 months to 23 years at a cellulose fiber plant where acetone was used as the only solvent found no significant excess risk of death from circulatory system disease or ischemic heart disease compared with rates for the U.S. general population (Ott et al. 1983a, 1983b). Industrial hygiene surveys found that median time-weighted-average acetone concentrations were 380,770, and 1,070 ppm based on job categories.

Reduced heart rates were observed in guinea pigs exposed to various high concentrations of acetone for various acute durations (Specht et al. 1939), but were probably a consequence of the narcotic effects of acetone (Section 2.2.1.4). Necropsy of the guinea pigs revealed no effects on the heart, but histological examination was not performed. Histological examination of the hearts of rats exposed intermittently to a high concentration of acetone (19,000 ppm) for 2-8 weeks revealed no evidence of treatment-related lesions (Bruckner and Peterson 1981b).

Gastrointestinal Effects. Case reports have described vomiting of blood and gastrointestinal hemorrhage in patients who had hip casts applied with acetone present in the setting fluid (Chatterton and Elliott 1946; Fitzpatrick and Claire 1947; Harris and Jackson 1952; Hift and Pate1 1961; Pomerantz 1950; Renshaw and Mitchell 1956; Strong 1944). As the vomitus contained blood several hours after vomiting first commenced, the gastrointestinal hemorrhage may have been due to the trauma of repeated vomiting. These patients had a strong odor of acetone in their breath, and acetone was detected in the urine and blood. These patients were exposed to acetone by inhalation during cast application and from evaporation from the casts after the applications. In addition, the possibility of contribution from dermal exposure could not be ruled out. In one case, exposure was considered to be mainly dermal (Hift and Pate1 1961).

Necropsy of guinea pigs that died after exposure to various high concentrations of acetone for various acute durations revealed no effects on the stomach (Specht et al. 1939), but histological examination was not performed.

Hematological Effects. In a health evaluation survey of 168 men and 77 women employed at a cellulose fiber production plant where acetone was used as the only solvent, all hematological parameters were within normal limits (Ott et al. 1983a, 1983c). The workers had been employed at the plant for at least 3 months to 23 years. Industrial hygiene surveys found median time-weighted-average acetone concentrations of 380, 770, and 1,070 ppm, based on job categories. Hematological effects have been observed in humans after inhalation exposure to acetone in controlled laboratory studies of volunteers. Statistically significant increased white blood cell counts and decreased phagocytic activity of neutrophils, compared with controls, were observed in the volunteers after a 6-hour exposure or repeated 6-hour exposures for 6 days to 500 ppm (Matsushita et al. 1969a, 1969b). No significant difference was seen in hematological parameters in the volunteers exposed to 250 ppm compared with controls. In contrast, hematological findings were within normal limits in volunteers exposed to 500 ppm for 2 hours (DiVincenzo et al. 1973) or $\leq$1,250 ppm acetone repeatedly for l-7.5 hours/day for as long as 6 weeks (Stewart et al. 1975).

In animals, no studies were located regarding effects on the formed elements of the blood after inhalation exposure to acetone.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to acetone.

Hepatic Effects. No indication that acetone caused hepatic effects in humans was found in controlled studies of volunteers. Clinical chemistry parameters indicative of liver injury (e.g., serum alanine aminotransferase, aspartate aminotransferase, lactic dehydrogenase, alkaline phosphatase, ornithine carbamoyl transferase, cholesterol, triglycerides, bilirubin, lipids, etc.) were within normal limits in volunteers exposed to acetone at concentrations of 500 ppm for 2 hours (DiVincenzo et al. 1973) or 11,250 ppm intermittently for various durations (Stewart et al. 1975). In a health evaluation survey of 168 men and 77 women employed for at least 3 months to 23 years at a cellulose fiber production plant where acetone was used as the only solvent, all clinical blood chemistry parameters (aspartate aminotransferase, alanine aminotransferase, lactic dehydrogenase, alkaline phosphatase, total

bilirubin, and albumin) were within normal limits (Ott et al. 1983a, 1983c). Industrial hygiene surveys found median time-weighted-average acetone concentrations of 380, 770, and 1,070 ppm, based on job categories.

Fatty deposits were found in the livers upon autopsy of guinea pigs that died after exposure to high concentrations of acetone for various acute durations (Specht et al. 1939). In contrast, intermittent exposure of rats to a high concentration of acetone (19,000 ppm) for 2-8 weeks did not produce signs of liver toxicity, assessed by the measurement of serum aspartate aminotransferase, lactic dehydrogenase, liver weights, and histological examination of the liver (Bruckner and Peterson 1981b).

Inhalation exposure to acetone at lower concentrations does not appear to be toxic to the liver of animals; however, acetone potentiates the hepatotoxicity induced by some other chemicals (see Section 2.6). The mechanism by which acetone exerts the potentiation is through the induction or increased activity of liver microsomal monooxygenases, particularly enzymes associated with cytochrome P-450IIEl (see Sections 2.35 and 2.6). Most of the studies showing enzyme induction have been conducted by the oral route (see Section 2.2.2.2). In acute inhalation studies in rats, acetone exposure resulted in statistically significant increases in the liver concentration of cytochrome P-450, the activity of ethoxycoumarin O-deethylase (associated with P-450IIBl), and the activity of glutathione-S-transferase, and decreased the liver free glutathione content (Brondeau et al. 1989; Vainio and Zitting 1978). Induction of microsomal enzymes is considered a normal physiological response to xenobiotics, rather than an adverse effect.

In a developmental study, mice exposed intermittently to 6,600 ppm acetone on gestational days 6-19 had significantly increased absolute and relative liver weights compared with controls ($p<0.05$) (NTP 1988). Increased liver weight is considered a sign of maternal toxicity in developmental studies. The increased liver weight could have been associated with enzyme induction.

Renal Effects. No indication that acetone caused renal effects in humans was found in controlled studies of volunteers. Clinical blood chemistry parameters indicative of kidney injury (e.g., blood urea nitrogen, uric acid) and urinalysis parameters were within normal limits in volunteers exposed to acetone at concentrations of 500 ppm for 2 hours (DiVincenzo et al. 1973) or ≤1,250 ppm intermittently for various durations (Stewart et al. 1975).

The only indication that inhalation exposure to acetone causes renal effects in animals was the consistent finding of congestion or distention of renal tubules or glomeruli in guinea pigs that died after exposure to high concentrations of acetone for various acute durations (Specht et al. 1939). Rats exposed intermittently to 19,000 ppm for ≤8 weeks had significantly decreased kidney weights ($p<0.0l$) after 4 weeks of exposure compared with controls, but not after 2 or 8 weeks of exposure or at 2 weeks postexposure (Bruckner and Peterson 1981b). Blood urea nitrogen levels were not affected by acetone exposure, and no evidence of histological changes in the kidneys were found. In the absence of other evidence of renal toxicity, the sporadically reduced kidney weight cannot be considered an adverse effect.

Derma/Ocular Effects. Eye irritation is a common complaint of workers exposed to acetone vapors occupationally (Raleigh and McGee 1972) and in volunteers exposed under controlled conditions (Matsushita et al. 1969a, 1969b; Nelson et al. 1943; Ross 1973). In a report of the experience at the Tennessee Eastman Corporation on acetone concentrations not associated with injury presented at the American Conference of Governmental Industrial Hygienists (ACGIH) Tenth Annual Meeting, it was noted that acetone is mildly irritating to the eyes at 2,000-3,000 ppm, with no irritation persisting after exposure ceases (Sallee and Sappington 1949). Lacrimation has also been observed in guinea pigs exposed to acetone vapors (Specht et al. 1939). Since eye irritation is due to direct contact of the eyes with the vapor rather than a true systemic effect of inhalation of the vapor, this and other dermal/ocular effects resulting from direct contact with acetone are discussed in Section 2.3.3.

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

Other systemic effects observed in animals after inhalation exposure to acetone include body weight changes. In a developmental study, rats exposed to acetone at 11,000 ppm, but not mice exposed to 6,600 ppm, intermittently during gestation had significantly ($p<0.05$) reduced body weight gain from gestational day 14 onward and reduced extragestational body weight on gestational day 20 (NTP 1988). However, in a behavioral study, no effect on body weight gain was observed in female rats exposed to 16,000 ppm intermittently for 2 weeks (Goldberg et al. 1964). It is possible that the condition of pregnancy made the rats more susceptible to body weight reduction. In addition, marked congestion and hemorrhage of the spleen were observed upon autopsy of guinea pigs that died after

exposure to various high concentrations of acetone for various acute durations (Specht et al. 1939). These effects could have been the consequence of death.

2.2.1.3 Immunological Effects

The only information regarding immunological effects in humans after inhalation exposure to acetone is the finding of statistically significant increased white blood cell counts, increased eosinophil counts, and decreased phagocytic activity of neutrophils in volunteers exposed to 500 ppm for a single 6-hour exposure or intermittently for 6 days (Matsushita et al. 1969a, 1969b). No significant difference in these parameters was seen in the volunteers exposed to 250 ppm compared with controls. Hematological parameters, including total white cell counts and differential white cell counts, were within normal limits in other volunteers exposed to 500 ppm for 2 hours (DiVincenzo et al. 1973) or $\leq$1,250 ppm acetone intermittently for durations in a study with a complex protocol (Stewart et al. 1975); however, these investigators did not examine the phagocytic activity of neutrophils. The NOAEL value of 250 ppm and LOAEL value of 500 ppm are recorded in Table 2-l and plotted in Figure 2- 1.

No studies were located regarding immunological effects in animals after inhalation exposure to acetone.

2.2.1.4 Neurological Effects

Case reports have described patients who became comatose or collapsed after hip casts were applied with acetone present in the setting fluid (Chatterton and Elliott 1946; Fitzpatrick and Claire 1947; Harris and Jackson 1952; Renshaw and Mitchell 1956; Strong 1944). In addition, a woman experienced headache, dizziness, weakness, difficulty speaking, and depression after a cast containing acetone had been applied (Pomerantz 1950). These patients had a strong odor of acetone in their breath, and acetone was detected in the urine and blood. These patients were exposed to acetone by inhalation during cast application and from evaporation from the casts after the applications. In addition, the possibility of contribution from dermal exposure could not be ruled out. In another case of neurological effects (drowsiness, fretfulness, irritability, restlessness, uncoordinated hand movement, nystagmus) developing after application of a cast, exposure was considered to be mainly dermal because an airblower was used continuously during the application to dissipate the fumes (Hift and

Pate1 1961). However, because the patient had kept his head under a blanket, some inhalation of acetone evaporating from the cast may have occurred.

Workers exposed to acetone in the past commonly experienced neurological effects. In an on-site medical appraisal of nine workers, in which the time-weighted average exposure concentration was 1,006 ppm, three of the workers mentioned headache and lightheadedness as subjective symptoms (Raleigh and McGee 1972). In another on-site medical appraisal of four workers, in which the time-weighted average exposure concentration was 901 ppm, none of the workers complained of neurological effects (Raleigh and McGee 1972). The medical examinations included the Romberg test, finger-to-nose test, and observations for nystagmus (involuntary rapid movement of the eyeball). These tests revealed no neurobehavioral effects in either study. Such symptoms as unconsciousness, dizziness, unsteadiness, confusion, and headache were experienced by seven workers exposed to >12,000 ppm acetone while cleaning out a pit containing acetone, that had escaped from nearby tanks (Ross 1973). The degree of the symptoms varied depending on the length of time that the workers had spent in the pit (2 minutes to 4 hours).

Neurological and behavioral effects have also been documented in volunteers tested under controlled laboratory conditions. These effects included general lack of energy and weakness, headache, delayed visual reaction time (Matsushita et al. 1969a, 1969b); subjective symptoms of tension, tiredness, complaints (not otherwise specified), and annoyance (Seeber and Kiesswetter 1991; Seeber et al. 1992); increases in response and the percent false negatives in auditory discrimination tests and increases in anger and hostility (Dick et al. 1989); and increased visual evoked response (Stewart et al. 1975). Other neurological and neurobehavioral tests (e.g., electroencephalography, choice reaction time, visual vigilance, dual task, memory scanning, postural sway, Romberg test, or heel-to-toe test) were also conducted on these volunteers, but acetone exposure had no effect on these parameters. The relationship between concentration and duration of exposure on the development of narcosis was demonstrated in volunteers exposed to acetone at 21,049-84,194 ppm for 1-8 hours (Haggard et al. 1944). As the concentration increased, the time to observations of signs of narcosis (not otherwise described), loss of righting reflex, and loss of cornea1 reflex decreased. It should be noted that these concentrations of acetone are extremely high, and exposure to lower concentrations of acetone for shorter durations has resulted in unconsciousness in some workers, as discussed above. Based on a LOAEL of 237 ppm for 4 hours for neurobehavioral effects in humans (Dick et al. 1989), an acute inhalation MRL of 26 ppm was calculated as described in footnote “b” in Table 2-l. Based on a

LOAEL of 1,250 ppm for neurological effects in a 6-week study (Stewart et al. 1975), intermediate and chronic inhalation MRLs of 13 ppm were calculated as described in footnote "c" in Table 2-l.

Narcotic effects have been observed in animals exposed acutely to acetone vapors. The narcotic effects observed in animals after inhalation exposure to acetone depend upon the duration and the magnitude of exposure. The narcotic effects appear to proceed through several stages: drowsiness, incoordination, loss of autonomic reflexes, unconsciousness, respiratory failure, and death as concentrations and durations increase. The acute data suggest that concentrations >8,000 ppm generally are required to elicit overt signs of narcosis, although neurobehavioral effects, when assessed by specific behavioral tests, have been observed at lower concentrations. The relationship between concentration and duration of exposure on the development of narcosis was demonstrated in rats exposed to acetone at 2,105-126,291 ppm for 5 minutes to 8 hours (Haggard et al. 1944). While exposure to 2,105 or 4,210 ppm for 8 hours resulted in no signs of narcosis or effects on righting reflex or cornea1 reflex, these effects were observed at higher concentrations. At increasing concentrations ≥10,524 ppm, the time to observations of signs of narcosis, loss of righting reflex, and loss of cornea1 reflex decreased. The responses were correlated with blood acetone levels. Similar concentration- and duration-response relationships were found in mice exposed to 16,839-84,194 ppm acetone for up to 4 hours (Mashbitz et al. 1936). Neurological responses included drowsiness, staggering, prostration, clonic movements of hind legs, and deep narcosis. Narcosis, evidenced by decreased respiratory and heart rates, paralysis, and coma were observed in guinea pigs exposed to 21,800 ppm continuously for periods ranging from 25 minutes to 24 hours (Specht et al. 1939). The degree of narcosis increased as the exposure duration increased. In a developmental study, virgin and pregnant mice experienced severe narcosis after a single 6-hour exposure to 11,000 ppm on the first day, but narcosis was no longer observed when the exposure was lowered to 6,600 ppm 6 hours/day for the rest of the study (NTP 1988).

Neurobehavioral effects, indicative of narcosis, have been observed in rats, mice, and baboons acutely exposed to acetone vapors. These effects include central nervous system depression measured by five tests of unconditioned performance and reflex in rats (Bruckner and Peterson 1981a), decreased operant behavior evaluated by a multiple fixed ratio-fixed interval schedule of food reinforcement in rats (Geller et al. 1979b), inhibition of avoidance behavior and escape response in rats (Goldberg et al. 1964), decreased response to food presentation in mice (Glowa and Dews 1987), decreased duration of immobility in a behavioral despair swimming test in mice (DeCeaurriz et al. 1984), and incoordination

in a "match to sample" operant behavioral test in baboons (Geller et al. 1979a). In these studies, the animals recovered from the neurobehavioral effects as exposure continued, indicating adaptation or tolerance, or after exposure ceased, demonstrating the reversibility of these effects. The length of the recovery period was generally related to the level of exposure (Bruckner and Peterson 1981a; Glowa and Dews 1987). In the experiments of Geller et al. (1979a, 1979b), only four baboons and three rats were studied, precluding meaningful statistical analysis, and only two of the four baboons exhibited the effects. The rats were exposed to 150 ppm for 0.5-4 hours, and the baboons were exposed to 500 ppm continuously for 7 days. Intermediate-duration intermittent exposure of rats to 19,000 ppm acetone resulted in a statistically significant decrease ($p<0.02$) in absolute brain weight, but no exposure-related histological lesions (Bruckner and Peterson 1981b). Thus, based on the available data, the neurological effects of acetone are reversible and cannot be attributed to histologically observable changes in the brains of animals or to electroencephalographic changes in humans.

The highest NOAEL values and the LOAEL values for neurological effects from each reliable study are recorded in Table 2-l and plotted in Figure 2- 1.

2.2.1.5 Reproductive Effects

Information regarding reproductive effects in humans after inhalation exposure to.acetone is limited. Premature menstrual periods were reported by three of four women exposed to 1000 ppm acetone for 7.5 hours in a laboratory study of volunteers (Stewart et al. 1975). The shortening of the menstrual cycle was considered to be possibly due to the acetone exposure. Women workers in a Russian factory where workroom levels of acetone ranged from 14 to 126 ppm were reported to have statistically significantly increased incidences of pregnancy complications, including miscarriage, toxicosis (not otherwise described), decreased hemoglobin levels and hypotension, and "weakness of labor activity," compared with controls (Nizyaeva 1982). However, the number of women studied, further description of the exposed and control groups (such as age, smoking history, use of alcohol), and description of workroom monitoring methods and statistical methods were not reported. Therefore, no conclusions can be made from this report. In a epidemiological study of the pregnancy outcome among 556 female laboratory workers, no statistically significant difference in the incidence of miscarriage was found between those exposed to a variety of solvents including acetone and those not exposed to solvents (Axelsson et al. 1984).

No reproductive effects (i.e., no effects on number of implants/litter, percent live pups/litter, or mean percent resorptions/litter) were observed in rats or mice in an inhalation developmental study (NTP 1988). No studies were located regarding reproductive effects in male animals, histological effects on reproductive organs of male or female animals, or the reproductive outcomes and other indices of reproductive toxicity in animals after inhalation exposure to acetone. The NOAEL values for reproductive effects in female rats and mice and the LOAEL value for premature menstrual periods in humans are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Developmental Effects

Information regarding developmental effects in humans after inhalation exposure to acetone is limited. Statistically significant increased incidences of developmental effects, such as, intrauterine asphyxia of fetuses and decreased weight and length of neonates, were reported for women workers in a Russian factory, where workroom levels of acetone ranged from 14 to 126 ppm (Nizyaeva 1982). However, the number of women studied, further description of the exposed and control groups (such as age, smoking history, use of alcohol), and description of workroom monitoring methods and statistical methods were not reported. Therefore, no conclusions can be made from this report. In a epidemiological study of the pregnancy outcome among 556 female laboratory workers, no statistically significant differences in the incidences of miscarriage, perinatal death rate, or malformations were found between those exposed to a variety of solvents, including acetone, and those not exposed to solvents (Axelsson et al. 1984).

In a development study in rats exposed intermittently to acetone during gestation, the only effect was a slight, but significant ($p<0.05$), decreased mean male and female fetal body weight at 11,000 ppm (NTP 1988). It should be noted that the dams exposed at this level had significantly ($p<0.05$) reduced body weight during gestation, reduced uterine weight, and reduced extragestational weight on gestational day 20. No effects were seen on sex ratio, incidence of fetal variations, reduced ossification sites, or mean fetal variations. The percent of litters with at least one fetal malformation was higher in the 11,000 ppm group than in the control group, but no statistically significant increased incidences of fetal malformations were observed. In mice similarly exposed during gestation, however, there was a slight, but significant ($p<0.05$) increase in percent late resorptions, decrease in mean male and female fetal weights, and increase in the incidence of reduced sternebral ossification in the 6,600 ppm group. The only evidence of maternal toxicity at this exposure level was statistically

significant increased absolute and relative liver weight. No effects were found on the number of implantations per litter, percent live fetuses/litter, sex ratio, incidence of malformations or skeletal variations combined. The NOAEL values and LOAEL values for developmental effects in rats and mice are recorded in Table 2- 1 and plotted in Figure 2-l.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to acetone. Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

In a retrospective mortality study of 948 employees (697 men, 251 women) of a cellulose fiber plant where acetone was used as the only solvent, no significant excess risk of death from any cause, including malignant neoplasm, was found when compared with rates for the U.S. general population (Ott et al. 1983a, 1983b). The workers had been employed at the plant for at least 3 months to 23 years. Industrial hygiene surveys found that median time-weighted-average acetone concentrations were 380, 770, and 1,070 ppm, based on job categories.

No studies were located regarding cancer in animals after inhalation exposure to acetone.

2.2.2 Oral Exposure

2.2.2.1 Death

The 1991 Annual Report of the American Association of Poison Control Centers National Data Collection System documented 1,137 incidents of human exposure to acetone (Litovitz et al. 1992). Of these incidents, 1,124 were due to accidental or intentional ingestion (the others were not clearly specified). No fatalities were reported, only three cases had a major medical problem, 364 were treated in a health care facility, 233 cases were referred to hospitals but had no effects, 367 cases

suffered minor effects, and 39 suffered from moderate effects. None of the major, minor, or moderate effects were further described, and the outcomes of the remainder of the incidents were not reported.

As seen in Table 2-2 and Figure 2-2, acute lethal dose (LD_{50}) values were located for rats, mice, and guinea pigs. In general, the lethality of acetone decreases with the age of the rats (Kimura et al. 1971). A higher LD_{50} value was found for young adult rats than for older adult rats, but the difference was not statistically significant. Higher LD_{50} values were found for Wistar rats (Smyth et al. 1962) and Nelson rats (Pozzani et al. 1959) than for Sprague-Dawley rats (Kimura et al. 1971). The LD_{50} value determined by Freeman and Hayes (1985), who also used Sprague-Dawley rats, is in line with values for 14-day-old and young adult Sprague-Dawley rats. An oral LD_{50} value of 5,250 mg/kg was found for male ddY mice (Tanii et al. 1986), and an oral LD_{50} value of 3,687 mg/kg was found for male guinea pigs (Striegel and Carpenter 1961). In a study to determine which doses to use in a developmental study, oral dosing of pregnant mice with acetone during gestation resulted in the death of one of four mice at 2,400 mg/kg/day, and the number of dead mice increased as the dose increased (EHRT 1987). No controls were used in the range-finding study. One of two rabbits given 7,844 mg/kg acetone by gavage died within 19 hours of dosing, two rabbits given 5,491 mglkg survived, while one rabbit given 3,922 mg/kg died in 96 hours (Walton et al. 1928). Oral doses of 7,500 or 8,000 mg/kg acetone were fatal to two puppies (Albertoni 1884). No controls were included in these studies, and the small numbers of animals used limits the reliability of the findings. Signs of narcosis usually precede death in animals (see Section 2.2.2.4). No information was located regarding the doses of acetone that could result in increased mortality after intermediate- or chronic-duration exposure.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, hematological, musculoskeletal, hepatic, renal, or dermal/ocular effects in humans after oral exposure to acetone. The systemic effects in humans and animals after oral exposure to acetone are discussed below. The highest NOAEL values and the LOAEL values for each systemic effect from all reliable studies are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. Oral exposure of animals to acetone has not been shown to produce adverse respiratory effects. However, microsomes from the lungs of hamsters exposed to acetone in drinking

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

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(G)	1 d 1x/d				1726 (LD_{50}-newborn rats) 4393 (LD_{50}-14-day old rats) 7138 (LD_{50}-young adult rats) 6667 (LD_{50}-older adult rats)	Kimura et al. 1971
2	Rat	(G)	once				9883 (LD_{50})	Pozzani et al. 1959
3	Rat	(G)	1 d 1x/d				8393 (LD_{50})	Smyth et al. 1962
4	Rat	(G)	1 d 1x/d				5800 (LD_{50})	Freeman and Hayes 1985
5	Gn pig	(G)	once				3687 (LD_{50})	Striegel and Carpenter 1961
6	Mouse	(G)	once				5250 (LD_{50})	Tanii et al. 1986
Systemic								
7	Human	(G)	once	Gastro		2241 (sore throat and erosion in mouth)		Gitelson et al. 1966
				Other			2241 (diabetes-like condition, hyperglycemia, polyuria, excessive thirst)	

TABLE 2-2. Levels of Significant Exposure to Acetone - Oral *(continued)*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
8	Rat	(W)	14 d	Hemato	4312		6942 (bone marrow hypoplasia)	NTP 1991; Dietz et al. 1991
				Hepatic	8560			
				Renal	8560			
				Other (body weight)	8560			
9	Rat	(G)	1 d 1x/d	Other		5800 (temporary 15% loss of body weight)		Freeman and Hayes 1985
10	Rat	(GW)	1 d 1x/d	Hepatic	1961			Plaa et al. 1982
11	Rat	(GW)	3 d 2x/d	Hepatic	392			Plaa et al. 1982
12	Rat	(GO)	1 d 1x/d	Hepatic Renal	871	871 (degeneration of apical microvilli in renal tubules)		Brown and Hewitt 1984
13	Rat	(W)	3-7 d	Other		3214 (reduced insulin stimulated glucose oxidation in epididymal fat)		Skutches et al. 1990
14	Rat	(GW)	2 d 3x in 2 d	Renal Other (body weight)	1766 1766			Valentovic et al. 1992
15	Rat	(GO)	1 d 1x/d	Hepatic	1177			Charbonneau et al. 1986b

TABLE 2-2. Levels of Significant Exposure to Acetone - Oral *(continued)*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
16	Mouse	(W)	14 d	Hepatic	1579	3896 (minimal to mild hepatocellular hypertrophy)		NTP 1991; Dietz et al. 1991
				Renal	12725			
				Other (body weight)	12725			
17	Mouse	(GW)	10 d Gd 6-15 1x/d	Other		3500 (reduced maternal body weight; [5%])		EHRT 1987
18	Mouse	(W)	10 d ad lib	Hepatic	1900			Jeffery et al. 1991
Neurological								
19	Human	(G)	once				2241 (coma, abnormal gait)	Gitelson et al. 1966
20	Rat	(G)	1 d 1x/d				5800 (prostration)	Freeman and Hayes 1985
Developmental								
21	Mouse	(GW)	10 d Gd 6-15 1x/d				3500 (decreased survival of pups)	EHRT 1987
Reproductive								
22	Mouse	(GW)	10 d Gd 6-15 1x/d				3500 (reduced reproduction index, increased gestation duration)	EHRT 1987

TABLE 2-2. Levels of Significant Exposure to Acetone - Oral *(continued)*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
INTERMEDIATE EXPOSURE								
Systemic								
23	Rat	(GW)	93-95 d 1x/d	Resp	2500			American Biogenics Corp. 1986
				Cardio	2500			
				Gastro	2500			
				Hemato	500	2500 (increased hemoglobin, hematocrit, mean cell hemoglobin, mean cell volume, decreased platelets)		
				Musc/skel	2500			
				Hepatic	500	2500 (increased serum alamine aminotransferase)		
				Renal	100	500 (increased severity of age-related nephropathy in males)		
				Derm/oc	2500			
				Other (body weight)	2500			
24	Rat	(GW)	46-47 d 1x/d	Hemato	500	2500 (increased hemoglobin, hematocrit, mean cell volume)		American Biogenics Corp. 1986
				Hepatic	500	2500 (increased serum alanine aminotransferase)		
				Other (body weight)	2500			
25	Rat	(W)	12 wk	Other (body weight)	732			Spencer et al. 1978

TABLE 2-2. Levels of Significant Exposure to Acetone - Oral *(continued)*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
26	Rat	(W)	6 wk	Other (body weight)	650			Ladefoged et al. 1989
27	Rat	(W)	13 wk	Resp	3400			NTP 1991; Dietz et al. 1991
				Cardio	3400			
				Gastro	3400			
				Hemato	200[b]	400 (mild macrocytic anemia)		
				Musc/skel	3400			
				Hepatic	3400			
				Renal	900	1700 (increased incidence and severity of nephropathy in males)		
				Derm/oc	3400			
				Other (body weight)	3400			
28	Mouse	(W)	13 wk	Resp	11298			NTP 1991; Dietz et al. 1991
				Cardio	11298			
				Gastro	11298			
				Hemato	11298			
				Musc/skel	11298			
				Hepatic	11298			
				Renal	11298			
				Derm/oc	11298			
				Other (body weight)	11298			
Neurological								
29	Rat	(GW)	93-95 d 1x/d		500	2500 (decreased brain weight, salivation)		American Biogenics Corp. 1986
30	Rat	(GW)	46-47 d 1x/d		500	2500 (excessive salivation)		American Biogenics Corp. 1986

TABLE 2-2. Levels of Significant Exposure to Acetone - Oral *(continued)*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
31	Rat	(W)	6 wk			650 (decreased motor nerve conduction velocity)		Ladefoged et al. 1989
32	Rat	(W)	12 wk		732			Spencer et al. 1978
33	Rat	(W)	13 wk		3400			NTP 1991; Dietz et al. 1991
34	Mouse	(W)	13 wk		11298			NTP 1991; Dietz et al. 1991
Reproductive								
35	Rat	(W)	6 wk		1071			Larsen et al. 1991
36	Rat	(W)	13 wk		1700		3400 (increased testis weight, decreased sperm motility, caudal weight and epididymal weight, increased incidence of abnormal sperm)	NTP 1991; Dietz et al. 1991
					3100 (female)			
37	Mouse	(W)	13 wk		4858 (male) 11298 (female)			NTP 1991; Dietz et al. 1991

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an intermediate oral minimal risk level (MRL) of 2 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

Cardio = cardiovascular; d = day(s); Derm/oc = dermal/ocular; (G) = gavage (vehicle not specified); (GW) = gavage water; (GO) = gavage oil; Gastro = gastrointestinal; Gd = gestation day(s); Gn pig = guinea pig; Hemato = hematological; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s)

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

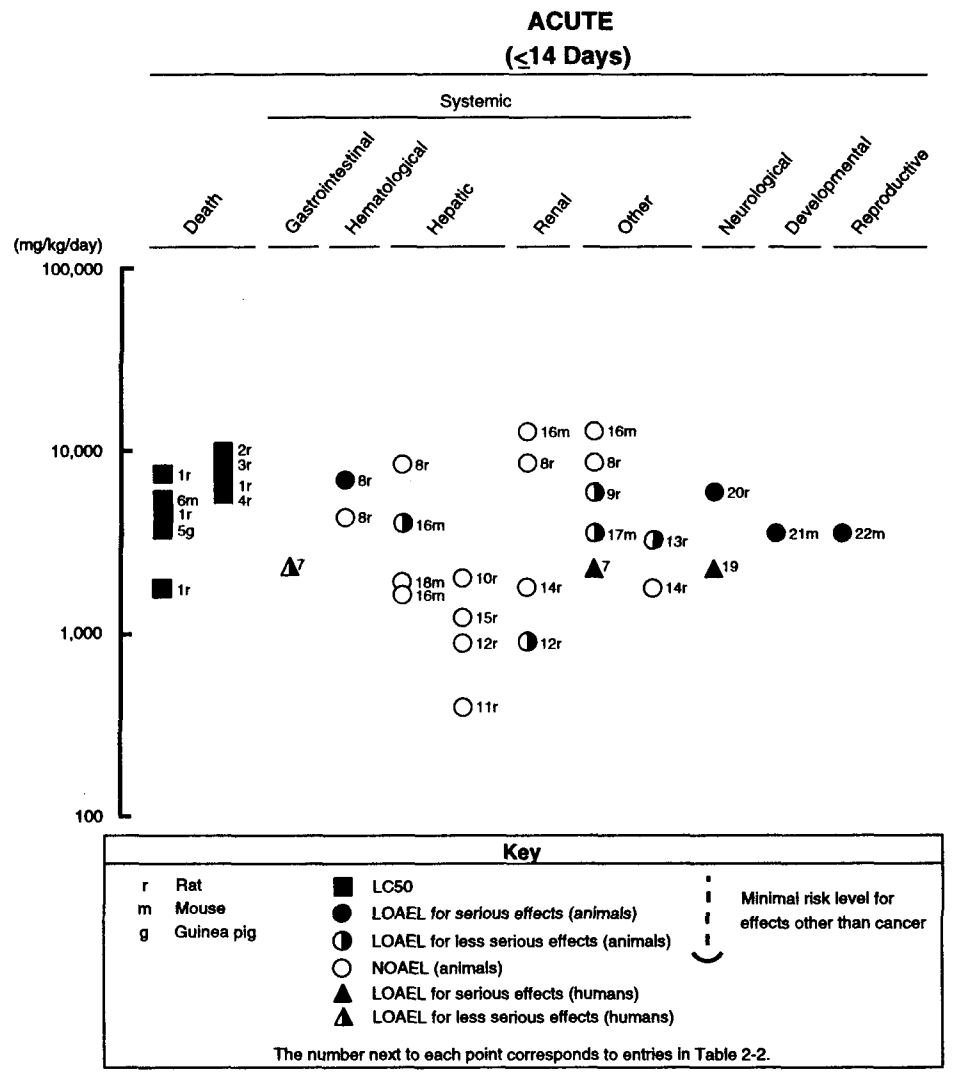
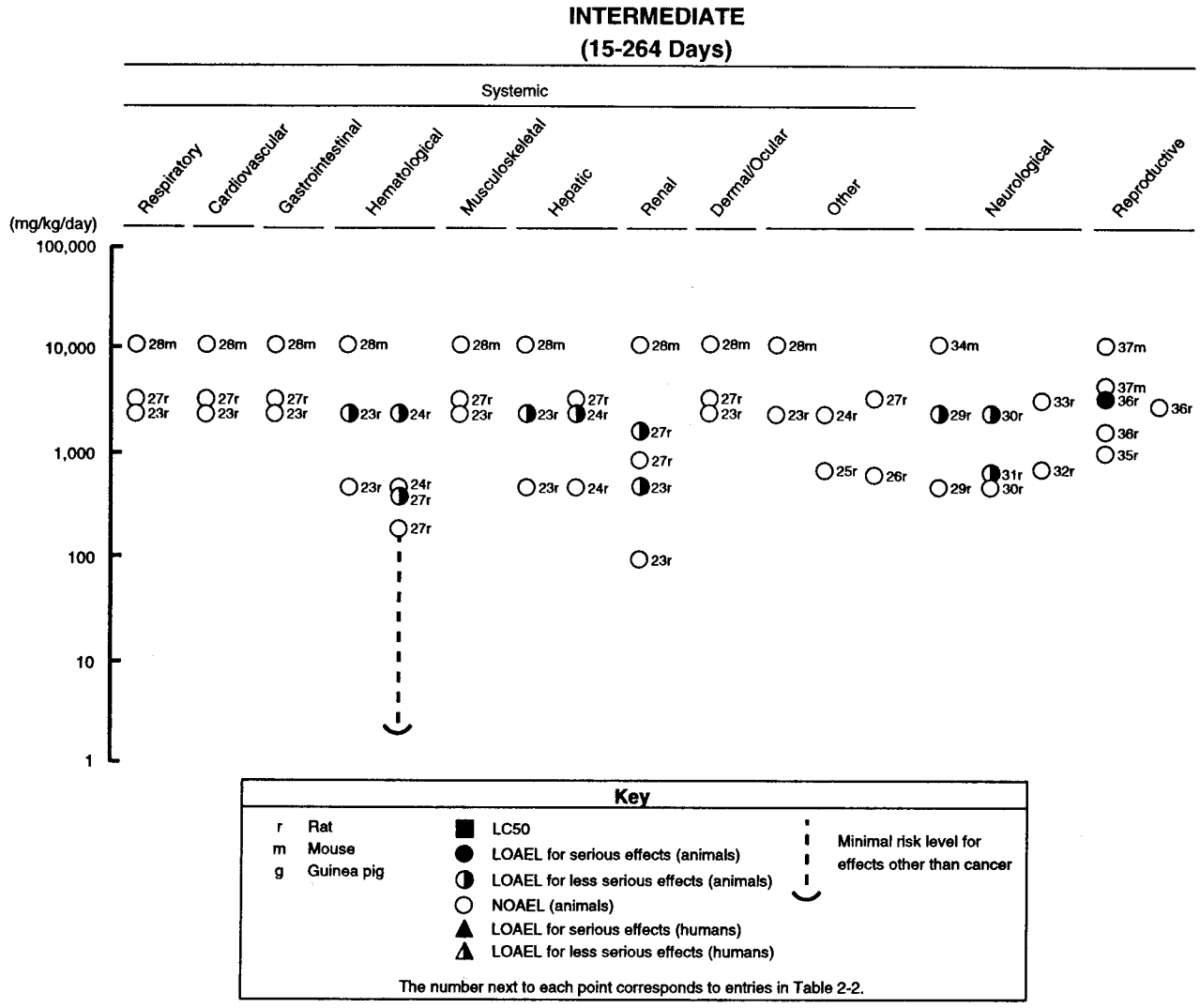


FIGURE 2-2. Levels of Significant Exposure to Acetone - Oral *(continued)*



water for 7 days had a 500% increased activity of aniline hydroxylase activity, an activity associated with cytochrome P-450IIEl (Ueng et al. 1991). Furthermore, the level of cytochrome P-45011El and the activity of butanol oxidase increased 6-fold in microsomes from the nasal mucosa of rabbits exposed to acetone in drinking water for 1 week (Ding and Coon 1990). Induction of microsomal enzymes is considered a normal physiological response to xenobiotics, rather than an adverse effect, unless accompanied by increased organ weight and histopathological or other adverse respiratory effects. Changes in respiratory rates (either increases or decreases), along with signs of narcosis, were observed in rabbits dosed with ≥3,922 mg/kg acetone (Walton et al. 1928), and irregular respiration, along with signs of narcosis, was observed in dogs dosed with 4,000 mg/kg (Albertoni 1884). In a range-finding study to determine which doses to use in a developmental study, mice that died at doses ≥4,800 mg/kg/day for 10 days displayed wheezing and/or rapid and labored breathing, accompanied by signs of severe narcosis, prior to death (EHRT 1987). However, the apparent respiratory effects probably reflect the severely compromised condition of these animals, rather than a toxic effect of acetone on the lungs. Gross necropsy of a dog dosed with 8,000 mg/kg acetone revealed no effects on the lungs, but the lungs were not examined histologically (Albertoni 1884). Histological examination of the lungs of rats and mice exposed to acetone in drinking water for 13 weeks (Dietz et al. 1991; NTP 1991) or of rats given acetone in water by gavage for 13 weeks (American Biogenics Corp. 1986) revealed no treatment related lesions. Thus, acetone by itself apparently is not toxic to the lungs of animals when administered by the oral route, but the induction of lung microsomal enzymes suggests that acetone may potentiate the respiratory effects induced by other chemicals (see Section 2.6).

Cardiovascular Effects. Oral exposure of animals to acetone has not resulted in adverse effects on the heart in intermediate-duration studies. Histological examination of the hearts of rats and mice exposed to acetone in drinking water for 13 weeks (Dietz et al. 1991; NTP 1991) or of rats given acetone in water by gavage for 13 weeks (American Biogenics Corp. 1986) did not reveal treatment- related lesions. However, the heart-to-brain weight ratio was significantly increased ($p<0.01$) in the female rats treated by gavage with 2,500 mg/kg/day. In the absence of histologically observable lesions, the toxicological significance of the increased heart weight is questionable.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects per se in humans after oral exposure to acetone, but a man who intentionally drank ≈200 mL of pure acetone

(≈2,241 mg/kg) had a red and swollen throat and erosions in the soft palate and entrance to the esophagus (Gitelson et al. 1966).

Significantly increased levels of cytochrome P-450IAl in duodenal microsomes and P-450IIB2 in duodenal and jejunal microsomes from rats exposed to acetone in drinking water for 3 days were found (Carriere et al. 1992). No increase in cytochrome P-450IIEl was found in these microsomal preparations. As discussed above for respiratory effects, induction of microsomal enzymes is considered a normal physiological response to xenobiotics rather than an adverse effect. Oral exposure of animals to acetone has not resulted in adverse effects on the gastrointestinal tract in intermediate-duration studies. Histological examination of the gastrointestinal tract of rats and mice exposed to acetone in drinking water for 13 weeks (Dietz et al. 1991; NTP 1991) or of rats given acetone in water by gavage for 13 weeks (American Biogenics Corp. 1986) did not reveal treatment-related lesions.

Hematological Effects. Exposure of rabbits to 863 mg/kg/day acetone in the drinking water for 7 days resulted in a 12.9-fold increase in the levels of cytochrome P-45011El in bone marrow microsomes (Schnier et al. 1989). As discussed for respiratory effects, induction of microsomal enzymes is considered a normal physiological response to xenobiotics rather than an adverse effect. Hematological effects of oral exposure to acetone have been observed in rats but not in mice. Bone marrow hypoplasia was observed in five of five male rats exposed to acetone in the drinking water for 14 days at 6,942 mg/kg/day, but not at 4,312 mg/kg/day (Dietz et al. 1991; NTP 1991). None of the female rats had bone marrow hypoplasia. Although mice were similarly treated for 14 days in this study, the authors did not specify whether bone marrow was examined; however, in the 13-week studies, no hematological effects or histologically observable lesions in hematopoietic tissues were found in mice. In contrast, evidence of macrocytic anemia was found in male rats exposed to acetone in drinking water for 13 weeks. This evidence consisted of significantly ($p<0.05$ or $p<0.01$) decreased hemoglobin concentration, increased mean corpuscular hemoglobin and mean corpuscular volume, decreased erythrocyte counts, decreased reticulocyte counts and platelets, and splenic hemosiderosis. The LOAEL for these effects was 400 mg/kg/day, and the NOAEL was 200 mg/kg/day. The number of affected parameters increased as the dose increased. Based on the NOAEL of 200 mg/kg/day for macrocytic anemia, an intermediate oral MRL of 2 mg/kg/day was calculated as described in the footnote in Table 2-2. In female rats, hematological effects consisted of statistically significant increased lymphocyte counts, increased mean corpuscular hemoglobin and mean corpuscular volume at the highest dose, and decreased platelets at the highest and next-to-highest dose levels (Dietz et al.

1991; NTP 1991). The biological significance of the hematological effects in female rats was not clear, but the effects were not consistent with anemia. Sex differences in the hematological effects of acetone exposure were also found in rats treated by gavage (American Biogenics Corp. 1986). Gavage treatment for 46-47 days significantly ($p<0.01$) increased hemoglobin, hematocrit, and mean cell volume in high-dose males (2,500 mg/kg/day), but not in females. With longer duration treatment (13 weeks), both high-dose males ($p<0.01$) and females ($p<0.05$) had increased hemoglobin and hematocrit, and high-dose males ($p<0.01$) also had increased mean cell hemoglobin and mean cell volume and decreased platelets. Thus, it appears that species and sex differences exist for hematological effects of oral exposure to acetone.

Musculoskeletal Effects. Histological examination of femurs of rats and mice exposed to acetone in drinking water for 13 weeks (Dietz et al. 1991; NTP 1991) or of rats given acetone in water by gavage for 13 weeks (American Biogenics Corp. 1986) did not reveal treatment-related lesions. Skeletal muscle was not examined histologically in the 13-week drinking water study (Dietz et al. 1991; NTP 1991), but histological examination of the skeletal muscle in rats in the 13-week gavage study did not reveal treatment-related lesions (American Biogenics Corp. 1986). Based on this limited information, it appears that acetone does not produce musculoskeletal effects.

Hepatic Effects. Acetone by itself is moderately toxic to the liver of animals, but acetone potentiates the hepatotoxicity of some other chemicals by inducing microsomal enzymes that metabolize other chemicals to reactive intermediates (see Sections 2.3.5 and 2.6). Numerous studies have investigated these mechanisms to identify the specific cytochrome P-450 isoenzymes involved (Banhegyi et al. 1988; Barnett et al. 1992; Carriere et al. 1992; Chieli et al. 1990; Furner et al. 1972; Gervasi et al. 1991; Hetu and Joly 1988; Hewitt et al. 1987; Hong et al. 1987; Hyland et al. 1992; Johannson et al. 1988; Kinsler et al. 1990; Kobusch et al. 1989; Koop et al. 1989, 1991; Menicagli et al. 1990; Porter et al. 1989; Puccini et al. 1989, 1990, 1992; Puntarulo and Cederbaum 1988; Robinson et al. 1989; Ronis et al. 1991; Ronis and Ingelman-Sundberg 1989; Schnier et al. 1989; Sipes et al. 1973; Song et al. 1989; Tu et al. 1983; Ueng et al. 1991; Yoo and Yang 1985). In these studies in general, rats, mice, rabbits, or hamsters were given acetone by gavage in water or in drinking water for 1 day to 2 weeks. Microsome preparations from the livers were then analyzed for cytochrome P-450 content, enzyme activities associated with specific cytochrome P-450 isoenzymes (particularly cytochrome P-450IIEl), and identification of the specific isoenzymes. Acetone has also been shown to increase the activity of glutathione S-transferase (Sippel et al. 1991). These topics are

discussed more fully in Sections 2.35 and 2.6. Induction of microsomal enzymes is considered a normal physiological response to xenobiotics rather than an adverse effect, unless it is accompanied by increased liver weight and other hepatic effects. Mice exposed to acetone in drinking water for 14 days had dose-related increased liver weights at ≥965 mg/kg/day, probably associated with microsomal enzyme induction (Dietz et al. 1991; NTP 1991). The increased liver weight was accompanied by hepatocellular hypertrophy at 23,896 mg/kg/day. In rats treated for 14 days, increased liver weight was stated to occur at the same or lower doses as in the 13-week study (see below), but more definitive information regarding the doses was not provided. Histological examination revealed no treatment-related hepatic effects in rats.

As stated above, acetone by itself is only moderately toxic to the liver. In mice exposed to 1,900 mg/kg/day acetone in the drinking water for 10 days, histological examination of the liver revealed no hepatic lesions (Jeffery et al. 1991). Acetone did not increase the level of serum alanine aminotransferase in rats at 871 mg/kg (Brown and Hewitt 1984), the levels of serum alanine aminotransferase or bilirubin at 1,177 mg/kg (Charbonneau et al. 1986b), or the activities of hepatic glucose-6-phosphatase, serum alanine aminotransferase, and serum ornithine carbamoyltransferase in rats given 1,961 mg/kg for 1 day or 392 mg/kg/day for 3 days (Plaa et al. 1982). However, in an intermediate-duration study, male rats, but not female rats, treated by gavage with 2,500 mg/kg/day, but not 500 mg/kg/day, for 46-47 days and for 13 weeks had statistically significant increased levels of serum alanine amino transferase (American Biogenics Corp. 1986). Liver weights were statistically significantly increased in female rats at ≥500 mg/kg/day, but not at 100 mg/kg/day, and in male rats at 2,500 mg/kg/day after 13 weeks, but organ weights were not measured in the rats treated for 46-47 days. In the 13-week drinking water study, liver weights were also significantly ($p<0.01$) increased in both sexes of rats at the same concentration (20,000 ppm, which was equivalent to 1,600 mg/kg/day for females, 1,700 mg/kg/day for males) and in female, but not male mice, at 11,298 mg/kg/day (Dietz et al. 1991; NTP 1991). However, in the mice, the increased liver weight was not associated with hepatocellular hypertrophy seen in the 14-day study, suggesting a development of tolerance.

Taken together, the data indicate that acetone induces liver microsomal enzymes, increases liver weights, and may cause liver injury, as evidenced by increased serum levels of liver enzymes associated with liver injury and hepatocellular hypertrophy. Species and sex differences exist in susceptibility to acetone-induced liver effects.

Renal Effects. Acetone can also induce enzymes in microsomes prepared from kidneys. In hamsters given drinking water containing acetone for 7 days (Ueng et al. 1991) or 10 days (Menicagli et al. 1990), the microsomes prepared from kidneys had increased levels of cytochrome P-450 and cytochrome b_5 and/or statistically significantly increased activities of p-nitrophenol hydroxylase, aniline hydroxylase, and aminopyrine-N-demethylase. Microsomes prepared from kidneys of rats treated by gavage with acetone had increased levels of cytochrome P-450IIEl and increased activity of N-nitrosodimethylamine demethylase (Hong et al. 1987). Induction of microsomal enzymes is considered to represent a normal physiological response to xenobiotics rather than an adverse effect, unless accompanied by increased organ weight and other adverse renal effects.

Oral exposure of rats and mice to acetone has resulted in effects on the kidney. Degeneration of the apical microvilli of renal tubules was reported in male rats after a single oral dose of acetone in corn oil, but not in corn oil treated controls (Brown and Hewitt 1984). The incidence of this lesion was not reported. However, in rats treated with 1,766 mg/kg/day acetone for 2 days, no significant difference was found for kidney weight, blood urea nitrogen (BUN) levels, or organic ion accumulation compared with controls (Valentovic et al. 1992). In 14-day drinking water studies, mice had doserelated increased kidney weights at $\geq$6,348 mg/kg/day (Dietz et al. 1991; NTP 1991). In rats treated for 16days, increased kidney weight occurred at the same or lower doses as in the 13-week study (see below), but more definitive information regarding the doses was not provided. Histological examination of the kidneys revealed no treatment-related lesions in rats or mice.

In the intermediate-duration drinking water study, significantly ($p<0.01$) increased kidney weights were seen in female rats at 21,600 mg/kg/day and in male rats at 3,400 mg/kg/day (Dietz et al. 1991; NTP 1991). Conversely, male, but not female rats, given acetone in the drinking water at 21,700 mg/kg/day had increased incidence and severity of nephropathy that was not accompanied by hyaline droplet accumulation (Dietz et al. 1991; NTP 1991). In the 13-week gavage study, kidney weights were significantly ($p<0.05$ or $p<0.01$) increased in female rats at $\geq$500 mg/kg/day and in male rats at 2,500 mg/kg/day (American Biogenics Corp. 1986). In addition, renal proximal tubule degeneration and intracytoplasmic droplets of granules (hyaline droplets) in the proximal tubular epithelium were seen in both control and treated rats at similar incidence, but the severity of these lesions showed a dose-related increase in males at $\geq$500 mg/kg/day and in females at 2,500 mg/kg/day. The renal lesions seen in both the gavage study and the drinking water study may represent an enhancement by acetone of the nephropathy commonly seen in aging rats (American Biogenics Corp.

1986; NTP 1991). No renal effects were observed in mice given acetone in the drinking water for 13 weeks (Dietz et al. 1991; NTP 1991).

Thus, species differences exist in susceptibility to acetone-induced renal effects. Sex differences also exist, with kidney weight increases occurring in female rats at lower doses than in males rats, but histopathological lesions occurring in male rats at lower doses than in females.

DermaVOcular Effects. No studies were located regarding dermal or ocular effects in humans after oral exposure to acetone.

Histological examination of eyes and skin of rats and mice after exposure to drinking water containing acetone for 13 weeks at doses $\leq$3,400 mg/kg/day (rats) and 11,298 mg/kg/day (mice) revealed no treatment-related effects (Dietz et al. 1991; NTP 1991). Similarly, ophthalmoscopic examination of the eyes of rats treated by gavage with acetone at doses $\leq$2,500 mg/kg/day revealed no ocular lesions (American Biogenics Corp. 1986). Skin was not examined histologically in the gavage study.

Other Systemic Effects. Acetone exposure of humans can result in diabetes-like symptoms, e.g., hyperglycemia and glycosuria. For example, a man who intentionally drank about 200 mL (about 2,241 mg/kg) of pure acetone had been treated at a hospital for acetone poisoning, but 4 weeks after the ingestion, he noticed excessive thirst and polyuria, and 2.5 months after ingestion, he was hyperglycemic (Gitelson et al. 1966). As discussed by Gitelson et al. (1966), hyperglycemia and glycosuria are commonly seen in cases of acetone poisoning.

Most of the information regarding other systemic effects in animals after oral exposure to acetone relates to body weight changes. However, in an acute study conducted to determine the temporal effects of maintaining elevated plasma concentrations of acetone similar to those encountered in fasting and diabetic patients, treatment of rats by gavage with 3,214 mg/kg/day resulted in significantly reduced ($p<0.01$) insulin-stimulated glucose oxidation in adipose tissue (Skutches et al. 1990). The reduction was greater in fasted rats than in fed rats. Rats treated by gavage with a lethal dose of acetone (LD_{50}= 5,800 mg/kg) lost 15% of their body weight until 48 hours after dosing (Freeman and Hayes 1985). However, treatment of rats by gavage with 1,766 mg/kg/day for 2 days (Valentovic et al. 1992) or with drinking water that provided lower doses ($\leq$1,200 mg/kg/day) for up to 2 weeks (Furner et al. 1972; Hetu and Joly 1988) did not affect body weight gain. Rats maintained on drinking

water for 14 days at higher doses displayed decreased body weight gain >l0% of controls, but the decrease was associated with reduced water consumption probably due to unpalatability (Dietz et al. 1991; NTP). In contrast, mice similarly treated had decreased water consumption at doses ≥6,348 mg/kg/day, but no effects on body weight gain occurred at doses ≤12,725 mg/kg/day. Maternal body weight was slightly (5%) but significantly (p=0.02) reduced on day 3 postpartum in mice treated with 3,500 mg/kg/day acetone by gavage during gestation (EHRT 1987).

In intermediate-duration studies, gavage or drinking water treatment of rats or mice with acetone did not result in reductions in body weight except in cases where fluid consumption was reduced (American Biogenics Corp. 1986; Ladefoged et al. 1989; NTP 1991; Spencer et al. 1978).

2.2.2.3 Immunological Effects

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

2.2.2.4 Neurological Effects

The narcotic effects of acetone occur after oral as well as inhalation exposure. Several case reports describe patients in minimally responsive, lethargic, or comatose conditions after ingesting acetone, but most of these cases are confounded by coexposure to other possible narcotic agents. For example, a 30-month-old child ingested most of a 6 ounce bottle of nail polish remover containing 65% acetone and 10% isopropyl alcohol (Gamis and Wasserman 1988); a known alcoholic woman ingested nail polish remover (Ramu et al. 1978); and a man ingested 200 mL of sake prior to intentionally ingesting liquid cement containing a mixture of polyvinyl chloride, acetone, 2-butanone, and cyclohexanone (Sakata et al. 1989). The lethargic and comatose condition of these patients were, however, attributed to acetone poisoning, although one case of coma was attributed primarily to cyclohexanol, the metabolite of cyclohexanone in the liquid cement (Sakata et al. 1989). Blood levels of acetone in some of these patients were 2.5 mg/mL (Ramu et al. 1978) and 4.45 mg/mL (Gamis and Wasserman 1988). In the case reported by Sakata et al. (1989), the blood level of acetone was 110 μg/L and the urine level was 123 μg/mL 5 hours after the ingestion, but the patient had been subjected to gastric lavage. A man who intentionally ingested about 200 mL of pure acetone (about 2,241 mg/kg) subsequently became deeply comatose, but responded to treatment (Gitelson et al. 1966). Six days

later, he was ambulatory, but a marked disturbance of gait was observed. This condition had improved upon follow-up examination 2 months later.

In acute experiments with animals, in which high oral doses of acetone resulted in death, severe neurological signs of toxicity preceded death. In a study to determine the LD_{50} value for acetone in rats (5,800 mg/kg), a state of prostration, usually without convulsions, preceded death (Freeman and Hayes 1985). In a study to determine which doses to use in a developmental study, oral dosing of pregnant mice with acetone during gestation resulted in languid behavior with subsequent death in one of four mice at 2,400 mg/kg/day (EHRT 1987). At higher doses, the number of mice dying increased, and they displayed a hunched appearance and became prostrate before death. No controls were used in this range-finding study. Rabbits dosed orally with 3,922, 5,491, or 7,844 acetone displayed signs of narcosis, the degree and the time to onset being dependent on dose (Walton et al. 1928). Signs of narcosis included weakness, depression, and unconsciousness. Puppies given 7,500 or 8,000 mg/kg and dogs given 4,000 mg/kg doses displayed incoordination, staggering, falling, tremors, delirium, prostration, and coma (Albertoni 1884). Dogs given 1,000 mg/kg showed no adverse effects. No controls were used in these studies, and only one or two animals were treated at each dose. A significant ($p<0.05$) reduction in nerve conduction velocity, but no effect on balance time in the rotorod test, was observed in rats treated for 6 weeks with acetone in drinking water at a dose of 650 mg/kg/day (Ladefoged et al. 1989). No reduction in nerve conduction velocity was found when tested at 3, 4, or 5 weeks of dosing. No histopathological lesions were found in tissues sampled from the cervico-medullary junction of the spinal cord; posterior tibia1 nerve proximal to the calf muscle branches; cerebellar vermis; thoracic, lumbar, and sacral spinal cord; L5 and L6 dorsal and ventral roots and spinal ganglia; and 3 levels of the sciatic nerve and the plantar nerves in the hindfeet of rats administered 732 mg/kg/day acetone in the drinking water for 12 weeks (Spencer et al. 1978). In another intermediate duration study, rats given 2,500 mg/kg/day acetone by gavage salivated excessively beginning on the 27th day of treatment (American Biogenics Corp. 1986). At the terminal sacrifice after 13 weeks of treatment, absolute brain weight was decreased in the male rats, but histological examination of the brain revealed no lesions. No clinical or histological evidence of neurotoxicity was observed in the rats or mice treated with higher doses for 13 weeks in the drinking water study (Dietz et al. 1991; NTP 1991). The fact that clinical signs of neurotoxicity were seen in the rats treated by gavage (American Biogenics Corp. 1986), but not in the rats or mice given higher doses in drinking water (NTP 1991), may reflect the intermittent nature of *ad libitum* dosing via drinking water, compared with the bolus nature of a gavage dose.

The highest NOAEL value and the LOAEL values for each species and duration category for neurological effects from all reliable studies are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to acetone. Reproductive effects were assessed in pregnant mice exposed by gavage to acetone during gestation (EHRT 1987). The reproductive index was significantly reduced ($p=0.05$) (number of females producing viable litters/number of surviving females that were ever pregnant; 24/31 treated compared with 34/36 controls). In addition, acetone treatment significantly ($p\leq0.01$) increased the duration of gestation from 18.1 days in controls to 18.5 days in treated mice.

No effects were observed on the fertility of male Wistar rats treated with drinking water containing acetone at 1,071 mg/kg/day for 6 weeks (Larsen et al. 1991). The indices of fertility examined were successful matings with untreated females, number of pregnancies, number of fetuses, testicular weight, seminiferous tubule diameter, and testicular lesions. However, male Sprague-Dawley rats treated with 3,400 mg/kg/day acetone in drinking water for 13 weeks had significantly increased ($p<0.01$) relative testis weight, probably because body weight was reduced, and significantly ($p<0.05$) decreased sperm motility, caudal weight and epididymal weight, and increased incidences of abnormal sperm (Dietz et al. 1991; NTP 1991). No testicular lesions were observed upon histological examination. Vaginal cytology examinations of the female rats revealed no effects. No effects on sperm morphology and vaginal cytology were observed in mice similarly treated with drinking water containing acetone at doses $\leq$4,858 mg/kg/day in males and $\leq$11,298 mg/kg/day in females.

The highest NOAEL values and the all LOAEL values in each species and duration category from all reliable studies are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to acetone.

In a reproduction study, treatment of pregnant mice during gestation with acetone significantly (≤10.01) reduced postnatal pup survival (EHRT 1987). The average weight of each live pup/litter was significantly reduced (p=0.0l) on postpartum day 0, but pups from the acetone treated groups gained significantly (p<0.0l) more weight than controls from postpartum day 0 to 3. As this study was not designed as a teratology study, fetuses or pups were not examined for internal malformations or skeletal anomalies.

The LOAEL value of 3,500 mg/kg/day for developmental effects in mice is recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to acetone.

Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals after oral exposure to acetone.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death of humans after dermal exposure to acetone.
In studies to determine the dermal LD_{50} values for acetone in rabbits (Roudabush et al. 1965; Smyth et al. 1962) and guinea pigs (Roudabush et al. 1965), the highest doses tested did not result in death. Therefore, LD_{50} values are >20 mL/kg (>15,688 mg/kg) for rabbits (Smyth et al. 1962) and >9.4 mL/kg (>7,373 mg/kg) for guinea pigs (Roudabush et al. 1965). No studies were located regarding death of animals after dermal exposure to acetone for intermediate- or chronic-durations.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, hematological, musculoskeletal, hepatic, or renal effects in humans after dermal exposure to acetone. Acetone has been used as a solvent or tested as a tumor promoter for other chemicals in skin painting studies in mice, and as the solvent control in these studies (Ward et al. 1986). An analysis of the histopathology in female SENCAR mice, used as acetone controls in a skin painting study of formaldehyde and held for up to 100 weeks of age, revealed no lesions associated with acetone exposure, that is, any lesions seen were considered spontaneous in this strain. Since all major tissues, gross lesions, and selected other (unspecified) tissues were examined histologically, it appears that no respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or dermal/ocular lesions were observed upon histological examination. The mice had been treated with 0.2 mL acetone on their backs twice a week for 92 weeks. The dose of 0.2 mL is recorded as a NOAEL value in mice for each systemic effect for chronic-duration exposure in Table 2-3. No other studies were located regarding respiratory, gastrointestinal, hematological, or musculoskeletal effects in animals after dermal exposure to acetone. The cardiovascular, gastrointestinal, and dermal/ocular effects in humans and the cardiovascular, hepatic, renal, dermal/ocular, and other systemic effects in animals after dermal exposure to acetone in other studies are discussed below.

Cardiovascular Effects. As discussed in Section 2.2.1.2, high pulse rates (120-160/minute) were commonly found in patients exposed to acetone by inhalation and/or dermally after application of casts for which acetone was used in the setting solution (Chatterton and Elliott 1946; Hift and Pate1 1961; Pomerantz 1950; Renshaw and Mitchell 1956). Amyloidosis was observed in the hearts of mice whose lumbo-sacral regions were painted twice weekly with an unspecified quantity of acetone for 12 months (Barr-Nea and Wolman 1977).

Gastrointestinal Effects. As discussed in Section 2.2.1.2, case reports have described vomiting of blood and gastrointestinal hemorrhage in patients who had hip casts applied with acetone in the setting fluid (Chatterton and Elliott 1946; Fitzpatrick and Claire 1947; Harris and Jackson 1952; Hift and Pate1 1961; Pomerantz 1950; Renshaw and Mitchell 1956; Strong 1944). In most cases, exposure was considered to be mainly by inhalation, but dermal exposure could not be ruled out. In one case, the exposure was considered to be mainly dermal (Hift and Pate1 1961).

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

Species	Exposure duration/ frequency	System	NOAEL	LOAEL (effect) Less serious	LOAEL (effect) Serious	Reference
ACUTE EXPOSURE						
Systemic						
Human	4-8 hr/d (occup)	Derm/oc		2000 ppm[a] (mild eye irritation)		Sallee and Sappington 1949
Human	2-3 d 8 hr/d	Derm/oc		901 ppm[a] (eye irritation)		Raleigh and McGee 1972
Human	1 d 2 min-4 hr/d	Derm/oc		12000 ppm[a] (eye irritation)		Ross 1973
Human	1 d 6 hr/d	Derm/oc		100 ppm[a] (eye irritation)		Matsushita et al. 1969b
Human	1 d 3-5 min/d	Derm/oc	200 ppm[a]	500 ppm[a] (eye irritation)		Nelson et al. 1943
Human	1 d 90 min/d	Derm/oc		1 mL (decreased protein synthesis)		Lupulescu and Birmingham 1975
Human	1 d 30 or 90 min/d	Derm/oc		1 mL (histological and ultrastructural degenerative changes in epidermis)		Lupulescu et al. 1972, 1973
Human	7 d 8 hr/d	Derm/oc		1006 ppm[a] (eye irritation)		Raleigh and McGee 1972
Rabbit	once	Derm/oc	0.01 mL			Smyth et al. 1962
Rabbit	once	Derm/oc			0.005 mL (severe eye necrosis)	Carpenter and Smyth 1941
Rabbit	once	Derm/oc			0.005 mL (severe corneal burn)	Smyth et al. 1962

TABLE 2-3. Levels of Significant Exposure to Acetone - Dermal *Continued)*

Species	Exposure duration/ frequency	System	NOAEL	LOAEL (effect) Less serious	LOAEL (effect) Serious	Reference
Rabbit	1 d 1 min/d	Derm/oc			20 (reversible corneal burns)	Bolkova and Cejkova 1983
Rabbit	1 d 3 min/d	Derm/oc		3.9 M (edema of eye mucous membrane)		Larson et al. 1956
Gn pig	1 d 25 min-23.4 hr/d	Derm/oc		21800 ppm[a] (lacrimation)		Specht et al. 1939
Mouse	once	Derm/oc		0.2 mL (slight increase in DNA synthesis in skin)		Iversen et al. 1988
INTERMEDIATE EXPOSURE						
Systemic						
Rabbit	3 wk 3 d/wk	Derm/oc	1.0 mL			Rengstorff et al. 1976
Rabbit	12-16 wk 1x/wk	Derm/oc		10 µL/wk (uveal melanocytic hyperplasia)		Pe'er et al. 1992
Gn pig	6 mo 5 d/wk 1x/d	Derm/oc Other		0.5 mL/d (mild erythema) 0.5 mL/d (transient weight loss of 60 g)		Taylor et al. 1993
Gn pig	3 wk 3 d/wk	Derm/oc			0.5mL (cataracts)	Rengstorff et al. 1972
Mouse	18 wk 2x/wk	Derm/oc		0.1 mL (moderate hyperplasia of epidermis)		Iversen et al. 1981

TABLE 2-3. Levels of Significant Exposure to Acetone - Dermal *Continued)*

Species	Exposure duration/ frequency	System	NOAEL	LOAEL (effect) Less serious	LOAEL (effect) Serious	Reference
CHRONIC EXPOSURE						
Systemic						
Mouse	92 wk 1x/wk	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc Other (all other tissues)	0.2 mL 0.2 mL 0.2 mL 0.2 mL 0.2 mL 0.2 mL 0.2 mL 0.2 mL 0.2 mL			Ward et al. 1986
Mouse	502 d 3x/wk	Derm/oc		667 (dermatits in 2/40, hyperplasia in 1/40, and hyper-keratosis in 1/40)		DePass et al. 1989
Reproductive						
Mouse	92 wk 1x/wk		0.2 mL			Ward et al. 1986

[a]Exposure to acetone vapor in air

Cardio = cardiovascular; d = day(s); Derm/oc = dermal/ocular; DNA = deoxyribonucleic acid; Gastro = gastrointestinal; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; min = minute(s); Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; occup = occupational; Resp = respiratory; wk = week(s); x = time(s)

Hepatic Effects. Amyloidosis was observed in the livers of mice whose lumbo-sacral regions were painted twice weekly with an unspecified quantity of acetone for 12 months (Barr-Nea and Wolman 1977).

Renal Effects. Amyloidosis was observed in the kidneys of mice whose lumbo-sacral regions were painted twice weekly with an unspecified quantity of acetone for 12 months (Barr-Nea and Wolman 1977).

Dermal/Ocular Effects. Liquid acetone has caused dermal effects in humans exposed by direct skin contact. Application of 1.0 mL directly to the skin of the forearms of six or seven volunteers for 30 or 90 minutes resulted in histological and ultrastructural degenerative changes in the epidermis (Lupulescu and Birmingham 1976; Lupulescu et al. 1972, 1973) and decreased protein synthesis (Lupulescu and Birmingham 1975) compared with untreated skin. The degenerative changes included a reduction and disorganization of the horny layers, intercellular edema, and vacuolization of the stratum spinosum. A laboratory technician being treated with squaric acid dibutyl ester in acetone for patchy alopecia areata on her scalp developed acute contact dermatitis after handling acetone for 2 years (Tosti et al. 1988). Patch testing with 10% acetone in olive oil showed a strong positive reaction (see Section 2.2.3.3).

Eye irritation is a common complaint of workers exposed to acetone vapors in the air at the workplace (Raleigh and McGee 1972) and in volunteers exposed to acetone in air under controlled laboratory conditions (Matsushita et al. 1969a, 1969b; Nelson et al. 1943). This eye irritation is due to direct contact of the eyes with the vapor rather than a systemic effect of vapor inhalation. Workers whose exposures to acetone in the workroom averaged $\geq$900 ppm complained of eye irritation (Raleigh and McGee 1972; Ross 1973). In controlled situations, the volunteers had been asked to give their subjective complaints, and some of the volunteers reported eye irritation after exposure to $\geq$100 ppm (Matsushita et al. 1969b). In a report of the experience at the Tennessee Eastman Corporation on acetone concentrations not associated with injury presented at the ACGIH Tenth Annual Meeting, it was noted that acetone is mildly irritating to the eyes at 2,000-3,000 ppm, with no irritation persisting after exposure ceases (Sallee and Sappington 1949).

Dermal effects have also been studied in animals after direct application of acetone to the skin. Application of 1.0 mL to the uncovered shaved skin of rabbits did not result in irritation within

24 hours (Smyth et al. 1962). Application of 0.2 mL acetone to the shaved skin of mice increased deoxyribonucleic acid (DNA) synthesis in the skin, compared to untreated shaved controls (Iversen et al. 1988). The increased DNA synthesis was considered a reaction to slight irritation. Moderate hyperplasia of the epidermis was observed in hairless mice treated twice weekly with 0.1 mL acetone for 18 weeks (Iversen et al. 1981). The hyperplasia persisted for 10 weeks after the end of treatment. Application of 0.5 mL/day for 6 months to the dorsal thorax of hairless guinea pigs resulted in only mild erythema at the site of application (Taylor et al. 1993). Amyloidosis was observed in the skin of mice whose lumbo-sacral regions were painted twice weekly with an unspecified quantity of acetone for 12 months (Barr-Nea and Wolman 1977). In a study in which acetone-treated mice were used as negative controls for a skin painting study of organosilanes, treatment with acetone alone 3 times/week for 502 days resulted in cases of hyperplasia (1 of 40), dermatitis (2 of 40), and hyperkeratosis (1 of 40) at the site of application (De Pass et al. 1989).

Ocular effects have been observed in animals after direct instillation of acetone into the eyes and after application of acetone to the skin. In rabbits, direct instillation of acetone into the eye has resulted in reversible cornea1 burns (Bolkova and Cejkova 1983), edema of mucous membranes (Larson et al. 1956), severe eye necrosis and cornea1 burns (Carpenter and Smyth 1946; Smyth et al. 1962), and uveal melanocytic hyperplasia (Pe'er et al. 1992). Application of 0.5 mL acetone directly to shaved skin of guinea pigs intermittently for 3 or 6 weeks resulted in cataract development (Rengstorff et al. 1972; Rengstorff and Khafagy 1985). In contrast, rabbits did not develop cataracts after application of 1.0 mL to the shaved skin intermittently for 3 weeks (Rengstorff et al. 1976). The difference in response between the guinea pigs and rabbits reflect species differences in susceptibility to the cataractogenic effects of acetone. Although the rabbits received twice as much acetone as the guinea pigs, the possibility that rabbits would have developed cataracts if an even larger quantity of acetone had been applied was not ruled out. However, no cataracts or lens opacities were found in hairless guinea pigs to which acetone (0.5 mL/day, 5 days/week) was applied to the skin for 6 months (Taylor et al. 1993). Genetic variability in susceptibility between the hairless guinea pigs (Taylor et al. 1993) and the normal guinea pigs (Rengstorff et al. 1972; Rengstorff and Khafagy 1985) is possible, but was believed to be unlikely (Taylor et al. 1993). Lacrimation was observed in guinea pigs exposed to acetone vapor in air at a concentration of 21,800 ppm for 25 minutes (Specht et al. 1939). The degree of lacrimation increased with longer exposure.

Other Systemic Effects. A transient weight loss of 60 g over a 2-week period was noted in hairless guinea pigs to which acetone was applied to the skin for 6 months (Taylor et al. 1993). Amyloidosis was observed in the adrenals and pancreas of mice whose lumbo-sacral regions were painted twice weekly with an unspecified quantity of acetone for 12 months (Barr-Nea and Wolman 1977).

2.2.3.3 Immunological Effects

The only information regarding immunological effects in humans after dermal exposure to acetone is a case report in which a laboratory technician being treated with squaric acid dibutyl ester in acetone for patchy alopecia areata on her scalp developed acute contact dermatitis after handling acetone for 2 years (Tosti et al. 1988). Patch testing with 10% acetone in olive oil showed a strong positive reaction. This acetone sensitization is considered a rare complication of sensitizing therapies for alopecia areata.

No studies were located regarding immunological effects in animals after dermal exposure to acetone.

2.2.3.4 Neurological Effects

As discussed in Section 2.2.1.4, case reports have described patients who became comatose or collapsed after hip casts were applied with acetone present in the setting fluid (Chatter-ton and Elliott 1946; Fitzpatrick and Claire 1947; Harris and Jackson 1952; Renshaw and Mitchell 1956; Strong 1944). In addition, a woman experienced headache, dizziness, weakness, difficulty speaking, and depression after a cast containing acetone had been applied (Pomerantz 1950). In another case of neurological effects (drowsiness, fretfulness, irritability, restlessness, uncoordinated hand movement, nystagmus) developing after application of a cast, exposure was considered to be mainly dermal because an airblower was used continuously during the application to dissipate the fumes (Hift and Pate1 1961). However, because the patient had kept his head under a blanket, some inhalation of acetone evaporating from cast may have occurred.

No studies were located regarding neurological effects in animals after dermal exposure to acetone.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after dermal exposure to acetone.

Acetone has been used as a solvent or tested as a tumor promoter for other chemicals in skin painting studies in mice, and as the solvent control in these studies (Ward et al. 1986). An analysis of the histopathology in female SENCAR mice, used as acetone controls in a skin painting study of formaldehyde and held for up to 100 weeks of age, revealed no lesions associated with acetone exposure, that is, any lesions seen were considered spontaneous in this strain. Since all major tissues, gross lesions, and selected other (unspecified) tissues were examined histologically, it is assumed that no lesions in the female reproductive organs were observed upon histological examination. The mice had been treated with 0.2 mL acetone on their backs twice a week for 92 weeks. However, the dose of 0.2 mL cannot be considered a NOAEL for reproductive effects in the absence of data on male reproductive organs or reproductive studies in animals after dermal exposure to acetone.

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after dermal exposure to acetone.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to acetone.

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans after dermal exposure to acetone.
Acetone has been used as a solvent for other chemicals in skin painting studies in mice, and as the solvent control in these studies (Ward et al. 1986). An analysis of the histopathology in female

SENCAR mice used as acetone controls in a skin painting study of formaldehyde and held for ≤100 weeks of age, revealed no neoplastic lesions associated with acetone exposure, that is, any lesions seen were considered spontaneous in this strain. Furthermore, acetone was negative as a tumor promoter for formaldehyde. In other skin painting studies in which acetone-treated mice were used as a negative vehicle control for organosilanes (De Pass et al. 1989) or flame retardants (Van Duuren et al. 1978), no evidence was found to suggest that acetone alone was a skin carcinogen. Acetone was also negative as a tumor initiator (Roe et al. 1972) and as a tumor promoter for 7,12-dimethylbenz[a]anthracene (Roe et al. 1972; Van Duuren et al. 1971; Weiss et al. 1986).

2.3 TOXICOKINETICS

Although the focus of this profile is on the effects of exposure to acetone from exogenous sources, a full understanding of the toxicokinetics requires consideration of the metabolic fate of endogenous acetone. Acetone is one of three ketone bodies that occurs naturally throughout the body (Le Baron 1982; Vance 1984). Under normal conditions, the production of ketone bodies occurs almost entirely within the liver and to a smaller extent in the lung and kidney (Gavin0 et al. 1987; Le Baron 1982; Vance 1984) The process is continuous, and the three products are excreted into the blood and transported to all tissues and organs of the body where they can be used as a source of energy. Two of these ketone bodies, acetoacetate and P-hydroxybutyrate, are organic acids that can cause metabolic acidosis when produced in large amounts. Acetone, in contrast, is nonionic and is derived endogenously from the spontaneous and enzymatic breakdown of acetoacetate (Kimura et al. 1986; Koorevaar and Van Stekelenburg 1976; Lopez-Soriano and Argiles 1985; Lopez-Soriano et al. 1985; Reichard et al. 1979; Van Stekelenburg and Koorevaar 1972). Endogenous acetone is eliminated from the body either by excretion into urine and exhaled air or by enzymatic metabolism (Charbonneau et al. 1986; Haggard et al. 1944; Owen et al. 1982; Reichard et al. 1986; Wigaeus et al. 1981). Under normal circumstances, metabolism is the predominant route of elimination and handles 70-80% of the total body burden.

Levels of endogenous acetone can fluctuate greatly due to normal diurnal variations (Wildenhoff 1972). In addition, circulating levels of endogenous acetone can fluctuate greatly depending on a person’s age (Paterson et al. 1967; Peden 1964), nutritional status and fasting (Jones 1987; Kundu et al. 1993; Levy et al. 1973; Lewis et al. 1977; Neiman et al. 1987; Reichard et al. 1979; Rooth and Carlstrom 1970; Williamson and Whitelaw 1978); and degree of physical activity (Koeslag et al.

1980). These physiological states all place high energy demands upon the body which result in increased fatty acid utilization and higher than normal blood levels of acetone. Infants and young children typically have higher acetone blood levels than adults due to their higher energy expenditure (Peden 1964). Pregnancy and lactation can also lead to higher than average blood levels of acetone (Bruss 1989; Paterson et al. 1967). In addition to these normal physiological conditions, a number of clinical states can result in humans acetonemia and acetonuria. In each of these conditions, the ketosis can be traced to the increased mobilization and utilization of free fatty acids by the liver. The conditions include diabetes (Kobayashi et al. 1983; Levey et al. 1964; Reichard et al. 1986; Rooth 1967; Rooth and Ostenson 1966), trauma (Smith et al. 1975), and alcoholism (Phillips et al. 1989; Tsukamoto et al. 1991).

Following exposure from exogenous sources, acetone is rapidly and passively absorbed from the lungs and gastrointestinal tract. Acetone can also be absorbed from the skin. After uptake by the lungs, acetone is readily absorbed into the bloodstream. Pulmonary uptake by humans has ranged from 30% to 80%. The reason for the wide range in reported values involves the unique aqueous wash-in/wash-out effect displayed when acetone is inhaled, causing spurious results. During this phenomenon, acetone, which is highly water soluble, will dissolve in epithelial cells during inspiration (wash-in) and evaporate during expiration (wash-out). This could account for lower than expected pulmonary absorption based on the high blood-air partition coefficient. Exhaled breath levels of acetone rise during exposure and reach steady state within 2 hours during exposure. Breath levels of acetone are directly proportional to the exposure concentration and duration and increase with physical activity due to increased pulmonary ventilation. Blood levels of acetone rose continuously during 2-4 hours exposure without reaching steady state, indicating continuous absorption during exposure. About 75-80% of the inspired amount is absorbed by blood within 15 minutes, and blood levels correlate with exposure concentration. Results in humans and animals indicate that relatively little acetone is absorbed from the nasal passages. No major differences were found between humans and animals in absorption after inhalation exposure. Based on animal studies, acetone is also absorbed rapidly and extensively from the gastrointestinal tract, with at least 74-83% absorbed based on the percent of the dose excreted by the lungs as acetone and carbon dioxide. As with inhalation, plasma levels rise proportionately with oral dose. Absorption can be delayed by the presence of fat in the stomach, due to delayed gastric emptying. Dermal absorption of acetone is also fairly rapid.

Acetone is highly water soluble and is widely distributed to tissues and organs throughout the body, especially to tissues with high water content. Radiolabeled unchanged acetone and total radioactivity (the percentage of total radioactivity that is not acetone represents metabolites) were detected in all tissues examined (blood, pancreas, spleen, thymus, heart, testis, vas deferens, lung, kidney, brain, liver, muscle, and adipose tissue) in male mice after inhalation exposure to radiolabeled acetone. Peak levels in these tissues occurred during the first 6 hours after exposure, and longer or repeated exposure resulted in no further accumulation except in liver and brown adipose tissue. Elimination of acetone from all tissues was complete within 24 hours, but total radioactivity, which represented metabolites, was still present in all tissues except blood and muscle. Thus acetone is not selectively distributed *to* any tissue and is not likely to accumulate with repeated exposure. Although information on distribution after oral and dermal exposure was not available, similar distribution is likely. Acetone can also undergo transplacental transfer to the fetus.

The metabolic fate of acetone, whether from endogenous or exogenous sources, is similar in humans and animals, is independent of route of exposure, and involves three separate gluconeogenic pathways, with ultimate incorporation of carbon atoms into glucose and other products of intermediary metabolism, with generation of carbon dioxide and adenosine triphosphate (ATP). Metabolism takes place primarily in the liver. Some of the exogenous acetone is unmetabolized and excreted primarily in the expired air. Acetone is initially oxidized to acetol by acetone monooxygenase, the rate limiting step governing the overall accumulation and elimination of acetone from the body. Acetol is oxidized to methylglyoxal by acetol monooxygenase. Both activities are associated with P-450IIE1, and the reactions require oxygen and nicotinamide adenine dinucleotide phosphate (NADPH). Methylglyoxal is converted to glucose directly or via D-lactate. Acetol can also be converted to L-1,2-propanediol, from which the pathways branch with either formation of L-lactate to D-glucose or degradation of 1,2-propanediol to acetate and formate. The carbon atoms of acetone can also be incorporated into glycogen, amino acids, fatty acid, heme, cholesterol, choline, and urea via acetate and formate. These pathways appear to operate in rats, mice, and rabbits, with very few species differences, and hence probably in humans. The relative importance of the three pathways depends upon the dose, with the methylglyoxal and lactate pathways predominating at low doses, but shunting to the formate-acetate branch of the propanediol pathway at higher doses as the methylglyoxal and lactate pathways become saturated. Physiological status, such as diabetes and fasting, and genetic status can alter the pattern of metabolism.

The main route of excretion is via the lungs regardless of the route of exposure with very little excreted in the urine. Acetone is excreted both unchanged and, following metabolism, mainly as carbon dioxide. In humans exposed by inhalation, the rate and pattern of respiratory and urinary excretion of acetone is influenced by exposure concentration, duration, the level of physical activity during exposure, and gender. Respiratory excretion is complete within 20 hours after inhalation, and peak urinary excretion occurs between 1 and 3.5 hours after exposure. The amount expired or excreted in the urine increases with increasing exposure concentration and with increasing duration of exposure, and increases with exercise during exposure. Women expired acetone more slowly than men, but the percentages excreted were not significantly different. The time for urinary excretion to be complete increases with exposure concentration and duration. Daily intermittent exposure may result in a slight residual body burden, but elimination is generally complete in 48-72 hours after the last exposure, depending on the exposure concentration. Excretion of acetone after inhalation exposure is better characterized in humans than in animals, but appears to be similar. In rats exposed to radiolabeled acetone, 52% of the expired radioactivity was unchanged acetone and 48% was carbon dioxide. Based on animal studies, excretion of acetone and carbon dioxide after oral exposure is similar to that after inhalation exposure.

Most of the toxic effects of acetone do not appear to be due to any of its metabolites. As is typical of solvents, acetone is irritating to the mucous membranes. Acetone is also narcotic, and although the mechanism by which acetone exerts is effects on the central nervous system is unknown, as a solvent, it may interfere with the composition of membranes, altering their permeability to ions. The mechanisms by which acetone produces hematological, hepatic, renal, reproductive, and developmental effects is unknown, but acetone has been found to distribute to all of these target organs, including the brain, and can undergo transplacental transfer. The renal toxicity may be due to the formation of formate and may involve α_{2u}-globulin. One of the main effects of acetone is the induction of microsomal enzymes, particularly cytochrome P-450IIEl. Enzyme induction is probably responsible for the increased liver and kidney weights observed in animals by virtue of the increase in protein content. Acetone also potentiates the toxicity of numerous other chemicals primarily by increasing their metabolism to toxic intermediates by the induction of cytochrome P-450IIE1, or otherwise interfering with their metabolism and elimination.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Due to its high blood-air partition coefficient (167-330) (Fiserova-Bergerova and Diaz 1986; Haggard et al. 1944; Paterson and Mackay 1989; Sato and Nakajima 1979), acetone is rapidly and passively taken up by the respiratory tract and absorbed into the bloodstream during inhalation exposure. Experiments in humans exposed to 23-4,607 ppm for up to 4 hours have measured pulmonary uptakes ranging from ≈30% to 80% (DiVincenzo et al. 1973; Landahl and Herrmann 1950; Nomiyama and Nomiyama 1974a; Pezzagno et al. 1986; Wigaeus et al. 1981). The reason for the wide range in reported values involves the unique aqueous wash-in/wash-out effect when acetone in inhaled, which can lead to spurious results (Schrikker et al. 1985, 1989). During this phenomenon, acetone, which is highly water soluble, will dissolve in epithelial cells during inspiration (wash-in) and evaporate during expiration (wash-out). This could account for the lower than expected pulmonary absorption based on the high blood/air partition coefficient (Wigaeus et al. 1981). Exhaled breath levels of acetone in humans rose during exposure and reached steady-state within ≈2 hours during exposure (Brown et al. 1987; DiVincenzo et al. 1973; Nomiyama and Nomiyama 1974a). Uptake was directly proportional to exposure concentration and duration (DiVincenzo et al. 1973; Wigaeus et al. 1981). Uptake also increased as the level of physical activity increased, i.e., during exercise, due to increased pulmonary ventilation (DiVincenzo et al. 1973; Haggard et al. 1944; Jakubowski and Wieczorek 1988; Wigaeus et al. 1981). Lungs (including the mouth and trachea) retained a greater percentage of inspired acetone (55%) than the nasal cavity (18%) in humans, indicating that the nasal cavity absorbs acetone less readily than the rest of the respiratory system (Landahl and Herrmann 1950). Blood levels of acetone rose rapidly during exposure for up to 4 hours with no indication that steady-state was reached (Brown et al. 1987; Dick et al. 1989; DiVincenzo et al. 1973), suggesting that during exposure, the rate of absorption exceeded the rate of distribution and elimination. In humans exposed to 100 or 500 ppm acetone for 2 or 4 hours, 75-80% of the amount of acetone inspired was absorbed by blood after 15 minutes of exposure, and 20-25% remained in the dead space volume (DiVincenzo et al. 1973). Higher inspired amounts resulted in higher blood levels (DiVincenzo et al. 1973; Haggard et al. 1944; Matsushita et al. 1969a; Pezzagno et al. 1986). A correlation between blood level at the end of exposure and exposure concentration was found in humans exposed to 23-208 ppm for 2-4 hours (Pezzagno et al. 1986). No significant difference in uptake or retention was found between men and women (Brown et al. 1987).

Animals also absorb acetone rapidly during inhalation exposure. Measurement of blood acetone levels in rats after 4-6 hours of exposure to various concentrations shows that blood levels correlate well with exposure concentrations (Charbonneau et al. 1986a, 1991; NTP 1988) and are highest immediately after exposure (NTP 1988). In rats exposed to 1.50 ppm for 0.5-4 hours, measurement of blood acetone concentrations during exposure revealed that blood levels increased steadily for 2 hours and then remained constant for the next 2 hours of exposure (Geller et al. 1979b). Blood acetone levels also correlated well with exposure concentration in dogs exposed for 2 hours (DiVincenzo et al. 1973). Blood levels were 4, 12, and 25 mg/L after exposures to 100, 500, and 1,000 ppm, respectively. Comparison of uptakes in dogs and humans revealed that humans absorbed a greater absolute quantity under comparable exposure conditions, but when expressed in terms of kg body weight, dogs absorbed 5 times more than humans. In anesthetized dogs allowed to inhale concentrated vapors of acetone spontaneously from a respirator at various ventilation rates, uptake by the respiratory tract was 52% at flow rates of 5-18 L/minute and 42% at ventilation rates of 21-44 L/minute (Egle 1973). Retention in the lower respiratory tract was 48% at 5-18 L/minute and 37.5% at 2140 L/minute. Retention by the upper respiratory tract was 57% at 4-18 L/minute. The effect of exposure concentration on total uptake was studied at a range of ventilation rates equated with exposure concentrations. Percent uptakes were 52.1% at a mean concentration of 212 ppm, 52.9% at 283 ppm, and 58.7% at 654 ppm. These results indicate the respiratory uptake of acetone by dogs is similar to human uptake values reported by Landahl and Herrmann (1950). The retention in the upper respiratory tract was higher than in the lower respiratory tract of dogs (Egle 1973). Exposure concentration had little effect on retention. The absorption of acetone by the nasal walls of anesthetized dogs, in which the nasal passage was isolated, increased when the airflow rate was increased (Aharonson et al. 1974). This suggests that increased airflow decreases the amount of acetone that reaches the lungs.

In rats exposed continuously to 2,210 ppm for 9 days, peak acetone blood levels of ≈ 1,020-l ,050 mg/L were reached in 3-4 days and remained at this level for the duration of exposure (Haggard et al. 1944) In rats exposed to 4,294 ppm for 12 days, acetone blood levels plateaued at 2,420-2,500 mg/L in 4 days. Blood levels in rats exposed to these concentrations for 8 hours/day were about half of those reached during continuous exposure. The amount of acetone absorbed in the first 8 hours exceeded the amount eliminated in the next 16 hours of exposure to fresh air, leading to a small accumulation. However, the accumulation during intermittent exposure did not reach the levels

achieved during continuous exposure. In other experiments of rats exposed to 2,105-126,291 ppm, the time to peak blood level decreased as the exposure concentration increased.

As was found in humans (Landahl and Herrmann 1950) and dogs (Egle 1973), disposition of acetone in the upper respiratory tract of rats, mice, guinea pigs, and hamsters indicates that relatively little acetone is absorbed from the upper respiratory tract (Morris 1991; Morris and Cavanagh 1986, 1987; Morris et al. 1986, 1991). The deposition efficiency was greater in Sprague-Dawley rats than in Fischer-344 rats. Deposition was similar in B6C3Fl mice and Fischer-344 rats, and greater than in Hartley guinea pigs and Syrian golden hamster. No difference was found between male and female Sprague-Dawley rats (Morris et al. 1991). The differences among strains and species could not be attributed to differences in metabolism because acetone is not significantly metabolized in the upper respiratory tract of these species (Morris 1991). Rather, the difference was attributed to differences in perfusion rates (Morris 1991; Morris and Cavanagh 1987).

2.3.1.2 Oral Exposure

In a series of experiments conducted in male volunteers given acetone orally at 40-80 mg/kg, an estimated 65-93% of the administered dose was eliminated via metabolism, with the remainder excreted in the urine and expired air in about 2 hours, indicating rapid and extensive gastrointestinal absorption (Haggard et al. 1944). In a human who ingested 137 mg/kg acetone on an empty stomach, the blood level of acetone rose sharply to a peak 10 minutes after dosing (Widmark 1919). In other experiments, the subject ingested the same dose 10 or 12 minutes after eating porridge. The blood acetone level rose slowly over 48-59 minutes to levels of about one-half to two-thirds that achieved after taking acetone on an empty stomach. Thus, the presence of food in the gastrointestinal tract lead to a slower rate of absorption.

Measurement of acetone in blood and urine of patients who accidentally or intentionally ingested acetone indicated that acetone was absorbed, but the percentage absorbed cannot be determined from the data. In one case, a man ingested liquid cement that provided a dose of acetone of ≈231 mg/kg (Sakata et al. 1989). His plasma acetone level was about 110 μg/mL and his urinary level was 123 μg/mL 5 hours after ingestion, but he had been subjected to gastric lavage. In a another case, a woman who had ingested nail polish remover had a blood acetone level of 0.25 g/100 mL (2.5 mg/mL) upon admission to the hospital (Ramu et al. 1978). The authors estimated that her body

burden was 150 g acetone at the time of admission. The serum acetone level of a 30-month-old child was 445 mg/l00 mL (4.45 mg/rnL) 1 hour after ingestion of a 6ounce bottle of nail polish remover (65% acetone) (Gamis and Wasserman 1988).

Experiments in rats indicated that acetone is rapidly and almost completely absorbed from the gastrointestinal tract after oral exposure. A rat given ^{14}C-acetone at a dose of 1.16 mg/kg expired 47.4% of the dose as ^{14}C-carbon dioxide over the 13.5-hour collection period (Price and Rittenberg 1950). Another rat given about 7.11 mg/kg ^{14}C-acetone by gavage once a day for 7 days expired 67-76% of the administered radioactivity as ^{14}C-carbon dioxide and 7% as ^{14}C-acetone over a 24-hour period after the last dose. From these data, absorption of least 74-83% of the administered dose can be inferred. A rat dosed with 6.19 mg/kg ^{14}C-acetone expired 4.24% of the radiolabel as unchanged ^{14}C-acetone over 5.5 hours, indicating rapid absorption. In rats given a single gavage dose of 1,177 mg/kg acetone, the maximum blood level of 850 μg/mL was reached in 1 hour and declined gradually to about 10 μg /mL over 30 hours (Plaa et al. 1982). In another experiment, peak blood levels and the time to peak blood levels were compared after various gavage doses to rats. After a dose of 78.44 mg/kg, the maximum blood level of acetone of about 200 μg/mL was reached in 3 hours and declined to 10 μg/mL at 12 hours, where it remained for the next 12 hours. After a dose of 196.1 mg/kg, the peak blood level was 400 μg/mL at 6 hours and declined biphasically to 50 μg/mL at 12 hours and to 30 μg/mL at 18 hours where it remained for the next 6 hours. After a dose of 784.4 mg/kg, the peak level was 900 μg/mL at 1 hour and declined to 300 μg /mL at 12 hours, 110 μg/mL at 18 hours, and 50 μg/mL at 24 hours. After a dose of 1,961 mg/kg, the peak level was 1,900 μg /mL at 3 hours and declined slowly to 400 μg /mL at 24 hours. In other studies where rats were given similar or higher doses of acetone, plasma acetone levels rose proportionately with dose in rats given acetone as single doses by gavage (Charbonneau et al. 1986a; Lewis et al. 1984) or in the drinking water for 7 days (Skutches et al. 1990).

In a study comparing the blood levels of acetone achieved after fasting with those after oral dosing, peak blood levels of acetone of about 35 and 110 μg /mL were reached within about 3 hours after dosing of rats with 78 and 196 mg/kg acetone, respectively (Miller and Yang 1984). The levels declined to near background levels within the next 16 hours. At an acetone dose of 20 mg/kg, the blood level increased to about 5 μg /mL over 19 hours, when the rats were sacrificed. In rats fasted for 48 hours, blood acetone levels increased continuously to about 13 μg /mL. While the maximal blood

concentrations of the treated rats differed considerably from that of the fasting group, the areas under the curve for the 78 and 196 mg/kg groups were comparable to the fasting groups.

Conflicting data were located regarding the effect of vehicle on the gastrointestinal absorption of acetone. In one study, maximum blood levels were higher and achieved earlier in rats given acetone by gavage in water than in rats given acetone by gavage in corn oil (Charbonneau et al. 1986a). The slower absorption of acetone in corn oil may have resulted from a delayed gastric emptying due to the presence of corn oil (fat) in the stomach. In a later study, however, very little difference in blood and liver levels of acetone were found in rats given the same dose of acetone in water or in corn oil (Charbonneau et al. 1991).

No studies were located regarding absorption of acetone in other animal species after oral exposure to acetone.

2.3.1.3 Dermal Exposure

Dermal absorption of acetone has been demonstrated in humans. Application of cotton soaked in acetone to a 12.5 cm^2 uncovered area of skin of volunteers for 2 hours/day for 4 days resulted in blood levels of acetone of 5-12 μg /mL, alveolar air levels of 5-12 ppm, and urinary concentrations of 8-14 μg /mL on each day (Fukabori et al. 1979). Higher blood, alveolar air, and urinary levels were obtained when the daily exposure increased to 4 hour/day: 26-44 μg /mL in blood, 25-34 ppm in alveolar air, and 29-41 μg /mL in urine. The absorption was fairly rapid, with peak blood levels appearing at the end of each daily application. Although precautions were taken to limit inhalation of acetone vapors, the authors noted that it was not possible to completely prevent inhalation, and the acetone concentration in the breathing zone of one subject was found to be 0.4-0.6 ppm. From the alveolar air and urine concentrations, it was estimated that a 2-hour dermal exposure was equivalent to a 2-hour inhalation exposure to 50-150 ppm, and a 4-hour dermal exposure was equivalent to a 2-hour inhalation exposure to 250-500 ppm acetone.

No studies were located regarding the absorption of acetone in animals after dermal exposure. The findings of cataract formation in guinea pigs exposed dermally (Rengstorff et al. 1972; Rengstorff and Khafagy 1985) (see Section 2.2.3.2) however, indicated that acetone was absorbed from the skin of the guinea pigs.

2.3.2 Distribution

Of eight samples of breast milk from lactating women from four urban areas, all were found to contain acetone (Pellizzari et al. 1982). Whether the source of acetone was endogenous or exogenous could not be determined. Nevertheless, the data indicate that acetone is distributed to mother's milk, and represents a source of excretion from the mother and exposure for infants. Acetone was identified in maternal and cord blood collected at the time of delivery, indicating transplacental transfer (Dowty et al. 1976).

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution of acetone or its metabolites in humans after inhalation exposure to acetone. However, acetone is well absorbed into the blood from the respiratory tract of humans (see Section 2.3.1 .l) and is highly water soluble. Therefore, widespread distribution, especially to tissues with high water content, is expected.

The distribution of acetone has been studied in mice exposed to acetone by inhalation (Wigaeus et al. 1982). Mice were exposed to 500 ppm ^{14}C-acetone for 1, 3, 6, 12, and 24 hours or for 6 hours/day for 1, 3, or 5 consecutive days, after which they were immediately killed. Radioactive unmetabolized acetone and total radioactivity were found in blood, pancreas, spleen, thymus, heart, testis, vas deferens, lung, kidney, brain, liver, muscle, brown adipose tissue, subcutaneous adipose tissue, and intraperitoneal adipose tissue. A common feature was an increase in tissue concentration of acetone and total radioactivity during the first 6 hours after exposure. These levels generally peaked from about 2.5 to 3.5 μmol/g tissue except in adipose tissues for total radioactivity. Peak levels of unmetabolized acetone were generally <l-l.3 μmol/g tissue. Exposure for longer than 6 hours resulted in no further accumulation of total radioactivity except in the liver and brown adipose tissue, in which levels rose to 4.8 μmol /g liver and 2.6 μmol /g brown adipose tissue at 24 hours. Only about 10% of the radioactivity in the liver at 24 hours was unmetabolized acetone. When the mice were exposed intermittently on 3 or 5 consecutive days, most tissues showed no or only a small additional increase in radioactivity after more than 1 day of exposure; however, the concentration in adipose tissue increased significantly with increasing exposure duration $\leq$5 days. The ratio of acetone in the tissues to that in blood was <1 at all exposure times except for the lungs (the site of exposure). However, the ratio of total radioactivity in the tissues to that in the blood showed that after 1 and

3 hours exposure, only the lung had a ratio >l, whereas the ratios in the kidneys and liver were >1 after 6 hours. Only the muscle and subcutaneous and intraperitoneal adipose tissue rose continuously. Elimination of acetone was fastest in blood, kidneys, lungs, brain, and muscles with half-times of about 2-3 hours during the first 6 hours after exposure. The slowest elimination was in subcutaneous adipose tissue with a half-time of >5 hours. Elimination of acetone was complete in all tissues by 24 hours after exposure, but total radioactivity, indicative of metabolites, was still present in all tissues except blood and muscle. These data indicate that acetone is not selectively distributed to any tissues but is more evenly distributed in body water. Acetone is not likely to accumulate with repeated exposure. The continued accumulation of radioactivity in the liver and brown adipose tissue could be the result of high metabolic turnover in these tissues.

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of acetone or its metabolites in humans or animals after oral exposure except that acetone was found in the liver of rats after oral exposure (Charbonneau et al. 1986a, 1991). However, acetone is well absorbed from the gastrointestinal tract (see Section 2.2.1.2) and is highly water soluble. Therefore, widespread distribution, especially to tissues with high water content, is expected.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of acetone or its metabolites in humans or animals after dermal exposure. The findings of cataract formation in guinea pigs exposed dermally (Rengstorff et al. 1972; Rengstorff and Khafagy 1985) (see Section 2.2.3.2), however, indicated that acetone was absorbed from the skin of the guinea pigs and distributed to the eyes.

2.3.2.4 Other Routes of Exposure

The finding of acetone and its metabolites in fetuses from rats injected intravenously with 100 mg/kg acetone on gestational day 19 indicates transplacental transfer (Peinado et al. 1986).

2.3.3 Metabolism

The metabolic fate of acetone is independent of route of administration and involves three separate gluconeogenic pathways, with ultimate incorporation of carbon atoms into glucose and other products and substrates of intermediary metabolism with generation of carbon dioxide. The metabolic pathways appear to be similar in humans and animals. The primary (major) pathway involves hepatic metabolism of acetone to acetol and hepatic metabolism of acetol to methylglyoxal, while two secondary (minor) pathways are partially extrahepatic, involving the extrahepatic reduction of acetol to L-1,2-propanediol. Some of exogenous acetone is unmetabolized and is excreted primarily in the expired air with little acetone excreted in urine (see Section 2.3.4).

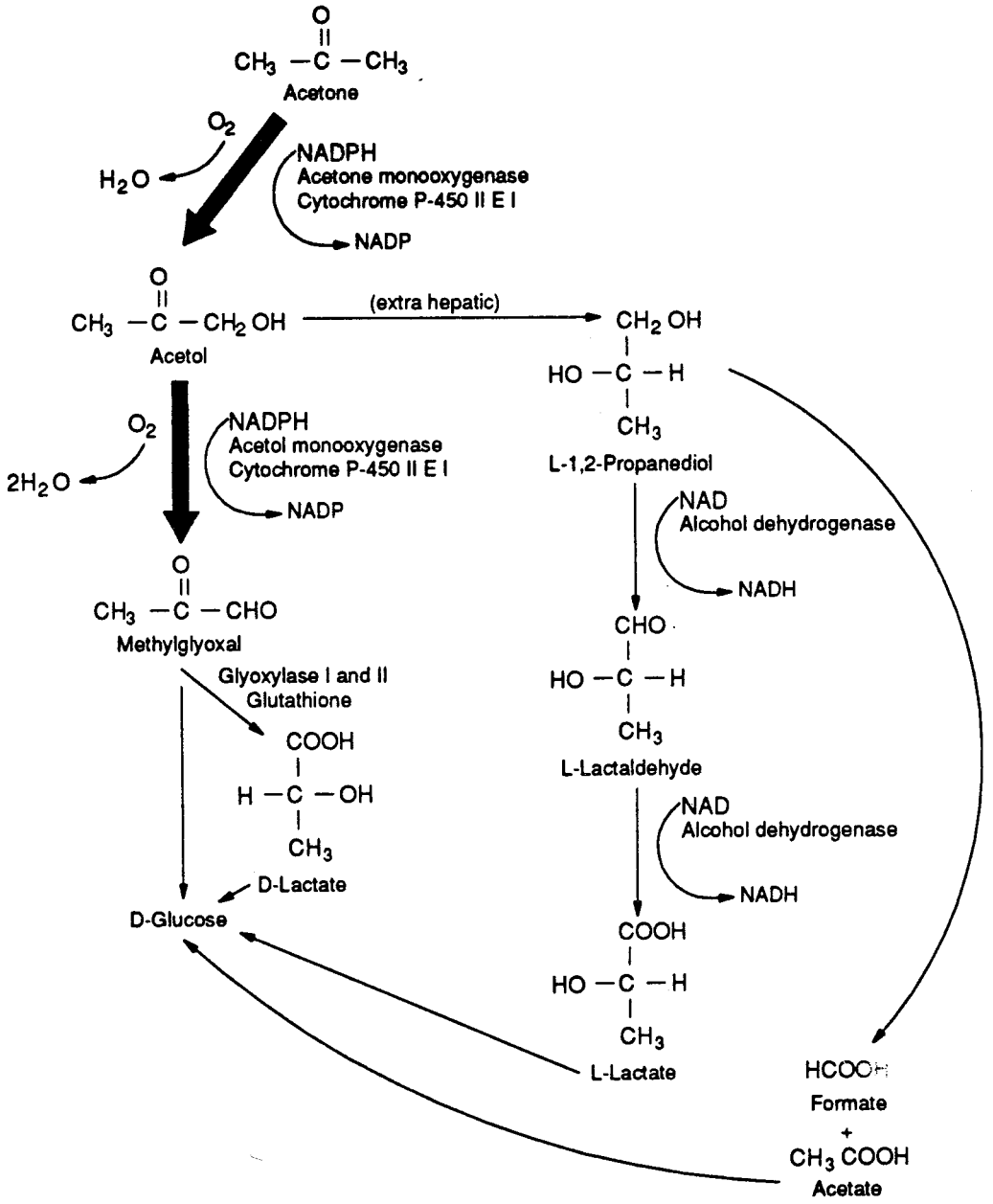
The only studies located regarding the metabolism of acetone in humans were conducted in normal fasted, obese fasted, and diabetic patients (Reichard et al. 1979; 1986). The involvement of gluconeogenesis was demonstrated in normal patients fasted for 3 days, obese patients fasted for 3 days, and obese patients fasted for 21 days before intravenous injection of 2-[^{14}C]-acetone (Reichard et al. 1979). The percentages of ^{14}C-glucose in plasma derived from ^{14}C-acetone were 4.2%, 3.1%, and 11.0% in the three respective groups, suggesting the involvement of gluconeogenesis. Cumulative ^{14}C-carbon dioxide excretion by the lungs during the a 6-hour collection period accounted for 17.4%, 21.5%, and 4.9% in the three respective groups. Radioactivity was also incorporated into plasma lipids and plasma proteins. Unmetabolized acetone in the expired air accounted for 14.7%, 5.3%, and 25.2%, urinary excretion of acetone accounted for 1.4%, 0.6%, and 1.3%, respectively, and *in vivo* metabolism accounted for 83.%, 94.1%, and 73.%, respectively, of the radioactivity. Intravenous infusion of 2-[^{14}C]-acetone into patients with diabetic ketoacidosis resulted in a mean plasma acetone turnover rate of 6.45 μmol /kg/minute (Reichard et al. 1986). Analysis of glucose in urine revealed a labeling pattern in five of the six patients consistent with the involvement of pyruvate in the gluconeogenic pathway. A different pathway may have operated in the other patient. Acetol and 1,2-propanediol were also detected in the plasma and the concentrations of these metabolites were directly related to the plasma level of acetone. The results demonstrated high plasma acetone levels in decompensated diabetic patients. The suggested pathway of acetone metabolism in these patients was acetone to acetol to 1,2-propanediol to pyruvate and ultimately to glucose, but other pathways may exist between subclasses of diabetic patients.

The metabolism of acetone has been studied extensively in animals, primarily in rats, and three separate pathways of gluconeogenesis have been elucidated (see Figure 2-3). These pathways are consistent with the metabolic fate of acetone in humans, discussed above. The elucidation of these pathways has been performed in experiments in which rats, mice, or rabbits were exposed by inhalation, by gavage, via drinking water, or by intravenous, subcutaneous, or intraperitoneal injection of nonradiolabeled acetone or to acetone labeled with ^{14}C in the methyl groups, number 2 carbon atom, or all three carbon atoms (Casazza et al. 1984; HaIlier et al. 1981; Hetenyi and Ferrarotto 1985; Johansson et al. 1986; Koop and Casazza 1985; Kosugi et al. 1986a, 1986b; Mourkides et al. 1959; Price and Rittenberg 1950; Puccini et al. 1990; Rudney 1954; Sakami and LaFaye 1950, 1951; Skutches et al. 1990). In these experiments, identification of metabolites in liver, plasma, or urine, the labeling patterns of ^{14}C incorporation into metabolites from ^{14}C-acetone in plasma or in liver, or the results of enzyme reactions using microsomes from acetone treated animals have led to the pathways illustrated in Figure 2-3.

In the first step, acetone is oxidized (hydroxylation of a methyl group) to acetol by acetone monooxygenase (also called acetone hydroxylase), an activity associated the cytochrome P-450IIE1, and requires oxygen and NADPH (Casazza et al. 1984; Johansson et al. 1986; Koop and Casazza 1985; Puccini et al. 1990). Cytochrome P-45011El can be induced by fasting, experimental diabetes, or exposure to ethanol or acetone (Johansson et al. 1988; Patten et al. 1986; Puccini et al. 1990). When the rate of acetone oxidation was evaluated in microsomes with acetone added to the incubation system, microsomes from rats (Johansson et al. 1986) and mice (Puccini et al. 1990) pretreated with acetone had a 7-8 times greater rate than microsomes from control rats or mice. Thus, acetone induces its own metabolism.

The formation of acetol is common to all three pathways. Subsequent conversion of acetol to methylglyoxal in microsomes is catalyzed by acetol monooxygenase (also called acetol hydroxylase), an activity also associated with cytochrome P-450IIE1, and also requires oxygen and NADPH (Casazza et al. 1984; Johansson et al. 1986; Koop and Casazza 1985). Methylglyoxal can then be converted to D-glucose by an unidentified pathway, and/or possibly by catalysis by glyoxalase I and II and glutathione to D-lactate, which is converted to D-glucose (Casazza et al. 1984). The conversion of methylglyoxal to D-lactate by the actions of glyoxalase I and II is well established (Racker 1951), but may represent a minor pathway in the metabolism of acetone (Casazza et al. 1984; Kosugi et al. 1986; Thornalley 1990). The unidentified pathway by which methylglyoxal is converted to D-glucose

FIGURE 2-3. Metabolic Pathways for Acetone*



*From Dietz et al. 1991; adapted from Casazza et al. 1984; Kosugi et al. 1986a

may involve conversion of methylglyoxal to pyruvate by 2-oxoaldehyde dehydrogenase, an activity identified using aqueous extracts of sheep liver acetone powders (Monder 1967).

In the second and third pathways, acetol is converted to L-1,2-propanediol by an extrahepatic mechanism that has not been characterized (Casazza et al. 1984; Kosugi et al. 1986a, 1986b; Rudney 1954; Skutches et al. 1990). The two pathways then diverge from the point of production of 1,2-propanediol. In the second pathway, 1,2-propanediol formed extra-hepatically returns to the liver where it is converted to L-lactaldehyde via nicotinamide adenine dinucleotide (NADH)-dependent alcohol dehydrogenase (Casazza et al. 1984; Kosugi et al. 1986a, 1986b), and L-lactaldehyde, in turn, is converted to L-lactate (Casazza et al. 1984; Ruddick 1972; Rudney 1954) via NADH-dependent aldehyde dehydrogenase (Casazza et al. 1984). L-lactate can then be converted to D-glucose (Casazza et al. 1984). In the third pathway, the L-1,2-propanediol formed extra-hepatically returns to the liver where it is degraded by an uncharacterized mechanism to acetate and formate (Casazza et al. 1984; Ruddick 1972).

Several studies have traced the labeling patterns of ^{14}C from 2-[^{14}C]-acetone or 1,3-[^{14}C]-acetone to gluconeogenic precursors and formate to incorporation of ^{14}C into glycogen, glycogenic amino acids, fatty acids, heme, cholesterol, choline, and urea (Mourkides et al. 1959; Price and Rittenberg 1950; Sakami and LaFaye 1950). The pattern of labeling suggested the involvement of the “acetate and formate” pathway. The ultimate fate of glucose is entry into glycolysis or into the tricarboxylic acid cycle, via pyruvate and acetyl coenzyme A (CoA) with the liberation of carbon dioxide, and subsequent electron transport and oxidative phosphorylation with the production of ATP (Lehninger 1970). Fatty acids, amino acids, and glycogen may also enter stages of intermediary metabolism.

The relative importance of the three pathways in the metabolism of acetone may depend upon the amount of acetone administered. When a trace amount of 2-[^{14}C]-acetone was administered intravenously to rats, the pattern of incorporation of ^{14}C into glucose was consistent with the production of glucose via the methylglyoxal/lactate pathway (Kosugi et al. 1986a). When a higher dose of 2-[^{14}C]-acetone (325 mg/kg) was injected, the pattern of incorporation was more consistent with the 1,2-propanediol pathway. These results suggest that at low doses of acetone or endogenous acetone, the methylglyoxal and lactate pathways predominate, but at higher doses, these pathways become saturated and metabolism is shunted to the formate-acetate branch of the 1,2-propanediol pathway.

In addition to the pathways illustrated in Figure 2-3, 2,3-butanediol (Casazza et al. 1984) and isopropyl alcohol (Lewis et al. 1984) were detected in the blood of rats after oral dosing with acetone, but their position in the metabolic scheme is not clear.

That acetone is extensively metabolized has been demonstrated by the finding of high percentages of ^{14}C-carbon dioxide in the expired air of animals exposed to ^{14}C-acetone (Mourkides et al. 1959; Sakami and LaFaye 1950, 1951; Price and Rittenberg 1950; Wigaeus et al. 1982) (see Section 2.3.4).

Although the liver is the primary site of acetone metabolism, radioactive unmetabolized acetone and total radioactivity were found in blood, pancreas, spleen, thymus, heart, testis, vas deferens, lung, kidney, brain, liver, muscle, brown adipose tissue, subcutaneous adipose tissue, and intraperitoneal adipose tissue of mice after inhalation exposure to ^{14}C-acetone (Wigaeus et al. 1982) (see Section 2.3.2.1). The fraction of total radioactivity that was not unchanged acetone represented metabolites. Elimination of acetone was complete in all tissues by 24 hours after exposure, but total radioactivity, indicative of metabolites, was still present in all tissues except blood and muscle. Whether these tissues (other than the liver) were capable of metabolizing acetone or whether the metabolites themselves were distributed to the tissues was not clear. However, microsomes from the lungs of hamsters exposed to acetone in drinking water for 7 days had a 500% increased activity of aniline hydroxylase activity, an enzyme associated with cytochrome P-450IIEl (Ueng et al. 1991). Furthermore, the level of cytochrome P-450IIEl increased 6-fold in microsomes from the nasal mucosa of rabbits exposed to acetone in drinking water for 1 week (Ding and Coon 1990). In hamsters given drinking water containing acetone for 7 days (Ueng et al. 1991) or 10 days (Menicagli et al. 1990), the microsome prepared from kidneys had increased levels of cytochrome P-450 and cytochrome b,. These results suggest that acetone metabolism, which involves cytochrome P-450IIE1, may occur in the lungs and kidneys of hamsters and the nasal mucosa of rabbits. Incubation of acetone with homogenates of nasal mucosa from mice indicated that acetone was metabolized via a NADPH-dependent pathway *in vitro*, but no evidence of *in vivo* metabolism of acetone by the upper respiratory tract was found in mice, rats, guinea pigs, or hamsters (Morris 1991). Injection of pregnant rats with acetone on gestational day 19 resulted in high levels of 1,2-propanediol and acetol in the fetuses (Peinado et al. 1986). Whether these findings reflect transfer of the metabolites from the dams or metabolism of transferred or endogenous acetone by the fetuses was not resolved.

Very few differences have been found among species in the metabolism of acetone. The pathways illustrated in Figure 2-3 appear to operate in rats, mice, and rabbits. In microsomes from rabbits exposed to acetone via drinking water, it was found that the oxidation of acetol could be catalyzed by cytochromes P-4503b (IIC3), 2 (IIB6), and 4(IA2), as well as by cytochrome P-4503a (P-450IIEl) (Koop and Casazza 1985). Only cytochrome P-450IIEl could catalyze the oxidation of acetone to acetol. No studies were located regarding the ability of other isoenzymes of P-450 to catalyze these reactions in other species.

Physiological or genetic status may alter the metabolism of acetone. When nondiabetic and diabetic rats were treated by gavage with acetone at doses of 1,000, 2,000, or 4,000 mg/kg, isopropyl alcohol was detected in the blood (Lewis et al. 1984). The levels of isopropyl alcohol and acetone increased with increasing dose in the diabetic rats, although with plateaus for both acetone and isopropyl alcohol at 1,000 and 2,000 mg/kg doses, but leveled off in the nondiabetic rats, indicating either saturation of the metabolic pathway from acetone to isopropyl alcohol or a reversibility of the conversion at high doses. It was suggested that in the diabetic rats, acetone and NADH, both needed for isopropyl alcohol production from acetone, presumably via alcohol dehydrogenase, may be diverted to gluconeogenic pathways to meet the diabetic rat's need for glucose, resulting in the short plateau. The subsequent rises of both compounds at the high dose of acetone in the diabetic rats could be accounted for by greater generation of NADH from fatty acid oxidation in the diabetic rat, which reduces acetone to isopropyl alcohol, accounting for the rising level of isopropyl alcohol. Liver homogenates from mice heterozygous for the obesity gene treated with acetone were more effective in converting acetone to lactate than liver homogenates from normal homozygous mice treated with acetone (Coleman 1980). The more effective conversion by heterozygous mice may account for their prolonged survival on the starvation regimen, compared with normal mice. In pregnant and virgin rats (either fed or fasted) injected intravenously with acetone, plasma acetol levels were not significantly different between fasted and nonfasted rats, but pregnant rats had significantly lower levels than virgin rats (Peinado et al. 1986). Liver levels of acetol were also significantly lower in pregnant rats than in virgin rats. Methylglyoxal levels were very high in the livers and plasma of nonfasted rats (pregnant or virgin), but fasting resulted in much lower levels. In contrast, no major differences were found in the expiration of carbon dioxide between fasted and diabetic rats injected intraperitoneally with acetone (Mourkides et al. 1959) or in the labeling pattern of ^{14}C derived from ^{14}C-acetone into glucose among nonfasted diabetic, fasted diabetic, normal nonfasted, and normal fasted rats injected intravenously with ^{14}C-acetone (Kosugi et al. 1986a, 1986b).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

The main route of excretion of acetone is via the lungs regardless of the route of exposure. Acetone is excreted both unchanged and, following metabolism, mainly as carbon dioxide. Studies have been conducted in humans exposed by inhalation, but these studies have followed the elimination only of unchanged acetone from blood and the excretion of unchanged acetone in the expired air and urine.

In humans exposed to acetone ≤1,250 ppm for ≤7.5 hours/day in a complex protocol for 16 weeks, the concentration of acetone in venous blood was directly related to the vapor concentration and duration of exposure, and inversely related to the time elapsed following exposure (Stewart et al. 1975). The rate of elimination of acetone from blood was constant regardless of blood acetone concentration (DiVincenzo et al. 1973). Half-times for blood elimination of 3-3.9 hours have been estimated in humans exposed to 100-500 ppm for 2-4 hours (Brown et al. 1987; DiVincenzo et al. 1973; Wigaeus et al. 1981). Elimination half-times of 3.9 hours and 6.2 hours have been estimated for arterial and venous blood, respectively (Wigaeus et al. 1981). No differences in elimination half-times were found between men and women (Brown et al. 1987). The elimination from blood was found to be complete in 24 hours after a 6-hour exposure in subjects exposed to 250 ppm, in 32 hours in subjects exposed to 500 ppm, and in 48 hours in subjects exposed to 1,000 ppm (Matsushita et al. 1969b). When humans were exposed for 6 hours/day for 6 days, the blood levels of acetone rose each day and declined to background levels by the following morning each day when the exposure concentration was 250 ppm (Matsushita et al. 1969a). At an exposure concentration of 500-ppm, however, the blood levels declined each day, but not to background levels. At the end of the 6-day exposure, blood acetone levels declined to background within 2 days for the 250 ppm group and within 3 days for the 500 ppm group. From the half-time and the data on time for decline to background levels, it appears that at higher concentrations, acetone may accumulate slightly in the blood during daily intermittent exposure, as would be experienced by workers.

The rate and pattern of respiratory excretion of acetone is influenced by exposure concentration, duration, the level of physical activity during exposure, and gender. In humans exposed to acetone ≤1,250 ppm for ≤7.5 hours/day in a complex protocol for ≤6 weeks, the rate of respiratory excretion was a function of the duration, and the concentration of acetone in breath after exposure was directly

related to the time-average concentration during exposure, with constant duration (Stewart et al. 1975). The length of time after exposure in which acetone could be detected in the expired air was related to the magnitude of exposure, with acetone still readily detectable 16 hours after exposure to 1,000 or 1,250 ppm for 7.5 hours. Excretion of acetone by the lungs was complete within 20 hours postexposure in humans exposed to 237 ppm for 4 hours (Dick et al. 1989). During exposure for 2 hours, the acetone concentration in expired air rose to 20 ppm in humans exposed to 100 ppm and to 90-100 ppm in those exposed to 500 ppm (DiVincenzo et al. 1973). After exposure to 100 ppm, the expired air concentration of acetone declined biphasically over the next 7 hours to 5 ppm. However, after exposure to 500 ppm, the expired air concentration dropped sharply to 2 ppm and declined to 1 ppm over the next 7 hours. Prolonging the exposure duration to 4 hours resulted in less than a 2-fold increase in acetone levels in postexposure expired air, which may reflect a greater loss of acetone through metabolism and urinary excretion. Exercise during the exposure period increased the elimination almost 2-fold. In humans exposed to acetone at rest, during exercise at a constant workload, or during exercise with step-wise increments in workload, expiration of acetone via the lungs amounted to 70, 80, and 200 mg, respectively, at 4 hours postexposure and to 50, 80, and 200 mg, respectively, over the next 4-20 hours (Wigaeus et al. 1981). Excretion of acetone from the lungs and kidneys (combined) amounted to 16, 20, and 27% of the amount absorbed in the three respective groups of subjects. Urinary excretion amounted to only 1% of the total uptake. Women expired acetone more slowly than men after a 4-hour exposure to 127-131 ppm, but the percentages excreted by the lungs were not statistically significantly different between men and women (17.6% for men, 15.0% for women) (Nomiyama and Nomiyama 1974b).

Very little unchanged acetone is excreted in the urine (DiVincenzo et al. 1973; Kawai et al. 1992; Vangala et al. 1991; Wigaeus et al. 1981). Urinary excretion is biphasic (Pezzagno et al. 1986). Peak urinary excretion occurred between 1 and 3.5 hours after exposure (Matsushita et al. 1969b; Wigaeus et al. 1981). In male volunteers exposed to 497 or 990 ppm acetone for 4 hours, cumulative acetone excretion in urine at 18 hours after cessation of exposure was 89.5 mg, suggesting slow excretion of acetone in the urine (Vangala et al. 1991). The amount of acetone excreted in the urine is influenced by the exposure concentration, the duration of exposure, and the level of physical activity during exposure. The acetone concentration in the urine ranged from 0-17.5 mg/L at the end of the 8-hour workshift in 45 workers exposed to 0-70 ppm acetone (background urinary concentration in 343 nonexposed subjects averaged 1.5 mg/L) (Kawai et al. 1992). Acetone levels in the preshift urine samples were significantly higher than background levels when acetone exposure on the previous day

was above 15 ppm. There was no significant difference between background urine levels and preshift urine levels when the previous day's exposure was ≤15 ppm. In humans exposed for 6 hours, peak urinary levels were found within the first hour after exposure and were 5.2 mg/dL in subjects exposed to 1,000 ppm, 2.9 mg/dL in subjects exposed to 500 ppm, and 1.8 mg/dL in subjects exposed to 250 ppm (Matsushita et al. 1969b). The decline in urinary acetone to background levels occurred within 48 hours for the 1,000 ppm group, within 32 hours for the 500 ppm group, and within 24 hours in the 250 ppm group. When human subjects were exposed for 6 hours/day for 6 days, urinary levels of acetone rose each day and declined to background levels by the following morning each day when the exposure concentration was 250 ppm (Matsushita et al. 1969a). At an exposure level of 500 ppm, however, urinary levels declined each day, but not to background levels. At the end of the 6-day exposure period, urinary acetone levels declined to background within 2 days for the 250 ppm group and within 3 days for the 500 ppm group. Therefore, excretion was more complete after exposure to lower concentrations, and at higher concentrations, acetone may accumulate somewhat during daily intermittent exposure, as would be experienced occupationally. Total 24-hour urine content of acetone was 1.25 mg in subjects exposed to 100 ppm for 2 hours and 3.51 mg in subjects exposed to 500 ppm for 2 hours (DiVincenzo et al. 1973). Prolonging the duration to 4 hours in 100 ppm group resulted in a total of 1.99 mg acetone in the urine. A slight increase in the urinary content of acetone (1.39 mg) was found when humans exposed to 100 ppm for 2 hours exercised during the exposure. The nature of physical activity during exposure also influenced the urinary excretion. At 3-3.5 hours after exposure, 8.5, 8.5, and 13.4 mg were excreted by the kidney in subjects exposed at rest, during exercise at a constant workload, and during exercise with step-wise increments in workload, respectively (Wigaeus et al. 1981). Urinary excretion amounted to only 1% of the total uptake.

As in humans, acetone is excreted mainly by the lungs of animals. Studies in animals have followed the elimination of acetone from blood and tissues, excretion of acetone and carbon dioxide in expired air, and the urinary excretion of formic acid.

Blood levels of acetone were highest immediately after a 4-hour exposure of rats to acetone (Charbonneau et al. 1986b). In rats exposed to 10,000 ppm, the blood level dropped from 2,114 to 5 μg /mL in 25 hours. In rats exposed to 15,000 ppm, the blood level dropped from 3,263 μg/mL to 50 μg /rnL after 25 hours. Elimination from blood was biphasic in rats exposed to 10,000 and 15,000 ppm, perhaps indicating saturation. Elimination from blood was triphasic in rats exposed to 1,000, 2,500, or 5,000 ppm and was complete within 17-25 hours. In dogs exposed to 100, 500, or

1,000 ppm acetone for 2 hours, blood levels declined in a log-linear manner with a half-time of 3 hours, similar to that observed in humans (DiVincenzo et al. 1973). Blood levels declined from 25 mg/L immediately after exposure to 10 mg/L at 5 hours postexposure for the 1,000 ppm group, from 12 to 3 mg/L for the 500 ppm group, and from 4 to 1.5 mg/L for the 100 ppm group. Elimination of radioactivity and ^{14}C-acetone was fastest from blood, kidney, lungs, brain, and muscle tissues of mice exposed to 500 ppm ^{14}C-acetone for 6 hours, with half-times of 2-3 hours during 6 hours postexposure (Wigaeus et al. 1982) (see Section 2.3.2.1). Elimination of acetone was complete in 24 hours in all tissues, but radioactivity (indicative of metabolites) was still present in all tissues except blood and muscle. When rats were exposed for 5 days, acetone tended to accumulate in adipose tissue.

Excretion of acetone in air followed pseudo-first-order kinetics in rats exposed to <20 ppm acetone for l-7 days, while at higher concentrations, saturation kinetics were observed (Hallier et al. 1981). In rats exposed to 500 ppm ^{14}C-acetone for 6 hours, 42 μmol of radioactive acetone and 37 μmol ^{14}C-carbon dioxide were excreted in the expired air during a 12-hour postexposure period, with 95% and 85%, respectively, recovered in the first 6 hours postexposure (Wigaeus et al. 1982). Radioactive acetone accounted for 52% and radioactive carbon dioxide accounted for 48% of the expired radioactivity. The concentration of acetone in the expired breath of dogs exposed to 100, 500, or 1,000 ppm acetone for 2 hours declined in a log-linear manner (DiVincenzo et al. 1973). The breath levels were directly related to the magnitude of exposure. Breath levels declined from 1.6 ppm at 30 minutes after exposure to 0.3 ppm at 300 minutes in the l00-ppm group, from 6.8 to 1.5 ppm in the 500-ppm group, and from 15 to 4 ppm in the l,000-ppm group.

Urinary excretion of formic acid was followed for 7 days in rats exposed to 62,000 ppm acetone for 2 days. The rate of formic acid excretion was 344 μg/hour compared with 144 μg /hour in controls (Hallier et al. 1981).

2.3.4.2 Oral Exposure

In volunteers who ingested 40-60 mg/kg acetone, the elimination of acetone in expired air and urine was determined 2 hours later, and a rate of metabolism of 1.82 mg/kg/hour along with the excretion data was used to calculate that 3.54-7.38 mg/kg had been excreted and metabolized (Haggard et al.

1944). The authors estimated that 65-93% of the administered dose was eliminated via metabolism, with the remainder excreted in the urine and expired air.

The only other information regarding excretion of acetone in humans after oral exposure is from case reports of accidental or intentional ingestion of materials containing acetone plus other components that may have influenced the elimination of acetone. In a man who ingested liquid cement containing 18% acetone (231 mg/kg), 28% 2-butanone, and 29% cyclohexanone and 720 mL sake, the plasma level of acetone was ≈1,120 μg /mL 5 hours after ingestion and declined to 65 μg /mL at 18 hours, 60 μg /mL at 24 hours, and <5 μg /mL at 48 hours (Sakata et al. 1989). A first-order plasma elimination rate constant of 0.038/hour and a half-time of 18.2 hours were calculated. The urinary level of acetone decreased gradually from about 123 μg /mL at 5 hours after ingestion to about 61 yg/mL at 19 hours. In a case of a known alcoholic who had ingested nail polish remover and whose blood acetone level was 0.25 g/dL (2.5 mg/mL) upon admission to the hospital, the blood level of acetone declined in a log-linear manner to about 0.06 g/dL (0.6 mg/mL) about 86 hours after admission, with a half-life of 31 hours (Ramu et al. 1978). The calculated clearance of acetone from the lungs was 29 ml/minute or 0.39 ml/minute/kg. A half-time of 25 hours for lung clearance was calculated, which is in agreement with the observed plasma elimination half-time of 31 hours. The serum acetone level of a 30-month-old child was 445 mg/100 mL (4.45 mg/mL) 1 hour after ingestion of a 6-ounce bottle of nail polish remover (65% acetone) and declined to 2.65 mg/mL at 117 hours, to 0.42 mg/mL at 48 hours, and to 0.04 mg/mL at 72 hours (Gamis and Wasserman 1988). The halftime of acetone in this patient was 19 hours in the severe early stage and 13 hours in later stages of intoxication, which suggested to the authors greater metabolism and/or excretion in children, compared with adults.

For animals, information regarding the excretion of acetone after oral exposure is available only for rats. As is the case after inhalation exposure, acetone, mainly as carbon dioxide, is excreted primarily by the lungs. In a rat given 1.16 mg/kg ^{14}C-acetone by gavage in water, expiration of ^{14}C-carbon dioxide totaled 47.4% of the administered radioactivity over the 13.5-hour collection period (Price and Rittenberg 1950). In another experiment, a rat was given 7.11 mg/kg radioactive acetone. A small amount of radioactive acetone (10%) was found in the expired air. Radioactive carbon dioxide and acetate were also detected. In a rat made diabetic by alloxan and given 6.15 mg/kg ^{14}C-acetone, a total of 7.29% of the administered radioactivity was expired as acetone and 51.78% as carbon dioxide. Radioactive acetate was detected in the urine. These data indicate that very little acetone (<10%) was

excreted by the lungs after small doses of acetone. A major fraction was oxidized to carbon dioxide and some of the derived carbon was used for acetylation. The diabetic rat was also able to oxidize acetone, but only to ≈70% of that in the normal rat.

The dose of acetone influences the elimination of acetone from blood (Plaa et al. 1982). At a dose of 78.44 mg/kg, the maximum blood level of 200 μg /mL at 3 hours declined to 10 μg /mL at 12 hours, where it remained for the next 12 hours (data inadequate to calculate total body clearance). At a dose of 196.1 mg/kg, the maximum blood level of 400 μg /mL at 6 hours declined biphasically to 50 μg /mL at 12 hours and to 30 μg /mL at 18 hours where it remained at 24 hours (total body clearance-64 ml/hour). At a dose of 784.4 mg/kg, the maximum blood level of 900 μg /mL at 1 hour declined to 300 μg /mL at 12 hours, to 110 μg /mL at 18 hours, and to 50 μg /mL at 24 hours (total body clearance-86 ml/hour). At a dose of 1,961 mg/kg, the maximum blood level of 1,900 μg /mL at 3 hours declined slowly to 400 μg /mL at 24 hours (total body clearance-75 ml/hour). Thus total body clearance was independent of dose, but the half-time for elimination increased from 2.4 hours for 196.1 mg/kg, to 4.9 hours for 784.4 mg/kg, and 7.2 hours for 1,96 1 mg/kg.

The vehicle (corn oil or water) in which acetone is administered has little influence on the elimination of acetone from blood (Charbonneau et al. 1986a). After gavage treatment of rats with 78, 196, 392, 784, or 1,177 mg/kg acetone in corn oil or water, elimination was biphasic for the two higher doses and triphasic for the lower doses. Acetone elimination from blood declined to <5 to <l0 μg /mL by 18-26 hours for all doses, but minor differences were found between water and corn oil as vehicle. The blood concentration curves from rats given acetone in water more closely resembled those from rats exposed by inhalation.

2.3.4.3 Dermal Exposure

Information regarding excretion of acetone after dermal exposure of humans is limited, but the main route of excretion is via the lungs, with little excreted in the urine. Application of an unspecified quantity of acetone to a 12.5 cm^2 area of skin of volunteers for 2 hours/day for 4 days resulted alveolar air levels of 5-12 ppm and urinary concentrations of 8-14 μg /mL on each day (Fukabori et al. 1979). These levels declined to background levels by the next day after each exposure. Higher alveolar air and urinary levels were obtained when the daily exposure increased to 4 hour/day:

25-34 ppm in alveolar air, and 29-41 μg /mL in urine, but these levels also returned to background each day.

No studies were located regarding excretion of acetone by animals after dermal exposure.

2.3.4.4 Other Routes of Exposure

As determined in humans, physiological status may influence the disposition of endogenous and exogenous acetone. In groups of nonobese patients fasted for 3 days, obese patients fasted for 3 days, and obese patients fasted for 21 days and injected intravenously with ^{14}C-acetone, 8-29% of the urinary acetone was derived from plasma radioactive acetone (Reichard et al. 1979). The concentrations of urinary acetone were 1.2, 0.4, and 2.6 μmol/mL in 3-day-fasted nonobese, 3-day-fasted obese, and 21-day-fasted obese patients, respectively. The rates of urinary acetone excretion were 1.2, 0.4, and 1.7 μmol/minute, respectively, suggesting marked renal reabsorption or backdiffusion. The percentages of measured acetone production that could be accounted for by excretion via the lungs were 14.7, 5.3, and 25.2%, respectively. The percentages that could be accounted for by urinary excretion were 1.4, 0.6, and 1.3%, respectively. Cumulative excretion of ^{14}C-carbon dioxide during the 6-hour turnover study periods accounted for 17.4, 21.5, and 4.9%, respectively. Thus, nonobese subjects fasted for 3 days excreted more acetone at higher rates than did obese subjects fasted for 3 days. However, excretion by the obese patients fasted for 21 days exceeded that by both 3-day-fasted groups. These differences are probably related to the effect that the degree of starvation ketosis has on the metabolism and overall disposition of acetone.

In contrast, no major differences were observed among normal rats, fasted rats, and diabetic rats in the excretion of ^{14}C-carbon dioxide from the lungs after intraperitoneal injections of ^{14}C-acetone (Mourkides et al. 1959). However, the dose level influenced the pattern of metabolism and, hence, the excretion of carbon dioxide. Rats that received 9.3-22.7 mg/kg radioactive acetone rapidly metabolized acetone, as evidenced by exhalation of 24-43% of the administered radioactivity as ^{14}C-carbon dioxide within the first 3 hours after dosing. Rats that received 258-460 mg/kg radioactive acetone exhaled only 2.1-5.7% of the radiolabel as carbon dioxide in the first 3 hours, 2.8-7.8% in the next 3-6 hours, and 16-29% in the next 6-24 hours. Rats injected subcutaneously with ^{14}C-acetone also excreted the derived radioactive carbon mainly as carbon dioxide. In rats fasted for 24 hours and given 170 mg/kg radioactive acetone, 27% of the radiolabel was excreted as carbon dioxide in 4 hours

(Sakami and LaFaye 1951). Rats fasted for 48 hours before the subcutaneous dose of 174 mg/kg radioactive acetone excreted 53% of the radiolabel as carbon dioxide over a 14-hour collection period (Sakami and LaFaye 1950).

Fasted pregnant rats had an enhanced capacity for acetone elimination compared with fasted or fed virgin rats or fed pregnant rats, after intravenous dosing with 100 mg/kg (Peinado et al. 1986). While the elimination of acetone from plasma was biphasic in all groups, the fasted pregnant rats eliminated acetone at a faster rate than the other groups.

2.3.5 Mechanism of Action

As discussed in the preceding sections, acetone is readily and passively absorbed from the lungs and gastrointestinal tract and probably from the skin. Since acetone is highly water soluble, it is readily taken up by the blood and widely distributed to body tissues. Other than gastric lavage in the case of ingestion, there is no known way to interfere with the absorption of acetone. Within the liver, acetone is metabolized by three separate gluconeogenic pathways through several intermediates, but most of its intermediate or final metabolites are not considered toxic. Unmetabolized acetone does not appear to accumulate in any tissue, but is excreted mainly in the expired breath. Acetone is irritating to mucous membranes, possibly due to its lipid solvent properties, resulting in eye, nose, throat, and lung irritation upon exposure to the vapors, and skin irritation upon dermal contact (see Section 2.2). The mechanism of the narcotic effects of acetone is not known, but as a solvent, acetone may interfere with the composition of the membranes, altering their permeability to ions (Adams and Bayliss 1968). Systemically, acetone is moderately toxic to the liver and produces hematological effects. The mechanism by which acetone produces these effects is unknown. The renal toxicity may be due to the metabolite, formate, which is known to be nephrotoxic (NTP 1991) and is excreted by the kidneys (Hallier et al. 1981). Furthermore, the renal toxicity, which appears to be specific for male rats, may involve $\alpha_{2\mu}$-globulin syndrome, as hyaline droplet formation was associated with the nephropathy observed in male rats in the American Biogenics Corp. (1986) study. Acetone also causes increases in liver and kidney weight, probably through the induction of microsomal enzymes, which would increase the weight of the organs by virtue of the increased protein content. Acetone also causes reproductive effects in male rats and is fetotoxic. Although the exact mechanism for many of the effects of acetone is not known, distribution studies in mice indicate that acetone and metabolites are found in all of the

target organs (Wigaeus et al. 1982). Acetone and some of its metabolites were also transferred to rat fetuses after the dams were exposed to acetone (Peinado et al. 1986).

One of the major effects of acetone is the potentiation of the toxicity of other chemicals (see Section 2.6). Pretreatment with acetone has been shown to potentiate the hepatotoxicity and nephrotoxicity of carbon tetrachloride and chloroform (Brown and Hewitt 1984; Charbonneau et al. 1985; 1986a, 1986b, 1988, 1991; Folland et al. 1976; Hewitt et al. 1980; Hewitt et al. 1987; Plaa et al. 1973, 1982; Plaa and Traiger 1972; Sipes et al. 1973; Traiger and Plaa 1972, 1974) by inducing particular forms of cytochrome P-450, especially cytochrome P-45OIIE1, and associated enzyme activities (Brady et al. 1989; Johansson et al. 1988; Kobusch et al. 1989). The induction of these enzymes leads to the enhanced metabolism of carbon tetrachloride and chloroform to reactive intermediates capable of causing liver and kidney injury. Acetone enhances the formation of carboxyhemoglobin by dichloromethane via induction of cytochrome P-450IIE1, leading to enhanced metabolism of dichloromethane to carbon monoxide (Pankow and Hoffmann 1989). Acetone also potentiates the hepatotoxicity of acetaminophen (Jeffery et al. 1991; Moldeus and Gergely 1980; Liu et al. 1991), N-nitrosodimethylamine and N-nitrosodiethylamine (Hong and Yang 1985; Lorr et al. 1984; Sipes et al. 1978;), thiobenzamide (Chieli et al. 1990), oxygen (Tindberg and Ingelman-Sundberg 1989), and chromate (Cr[VI]) (Mikalsen et al. 1991); the genotoxicity of N-nitrosodimethylamine (Glatt et al. 1981; Yoo and Yang 1985; Yoo et al. 1990); the hematotoxicity of benzene (Johansson et al. 1988; Johansson and Ingelman-Sundberg 1988; Schnier et al. 1989); and the lethality of acetonitrile (Freeman and Hayes 1985; 1988) by inducing cytochrome P-450IIEl. The hepatotoxic and nephrotoxic effects of dibromochloromethane and bromodichloromethane (Hewitt et al. 1983) and the hepatotoxic effects of 1,l ,Ztrichloroethane (MacDonald et al. 1982a, 1982b), 1, 1-dichloroethene (Hewitt and Plaa 1983; Jaeger et al. 1975), and dichlorobenzene (Brondeau et al. 1989) are also enhanced by acetone. The exact mechanisms for these interactions are not clear, but the involvement of mixed function oxidases has been implicated. The renal toxicity of N-(3,5-dichlorophenyl) succinimide (a fungicide) is potentiated by acetone by the induction of cytochrome P-450IIEl (Lo et al. 1987).

In other interactions, acetone enhances the neurotoxicity of ethanol by a proposed mechanism whereby acetone inhibits the activity of alcohol dehydrogenase, a reaction responsible for 90% of the elimination of ethanol (Cunningham et al. 1989). Acetone also potentiates the neurotoxicity and reproductive toxicity of 2,5-hexanedione (Ladefoged et al. 1989; Lam et al. 1991; Larsen et al. 1991).

The exact mechanism for these interactions is not clear but appears to involve decreased body clearance of 2,5-hexanedione by acetone (Ladefoged and Perbellini 1986).

These interactions and mechanisms are discussed more fully in Section 2.6.

2.4 RELEVANCE TO PUBLIC HEALTH

Acetone is a highly volatile, highly water-soluble aliphatic ketone. Acetone is readily absorbed by the lungs and gastrointestinal tract, taken up the blood, and widely distributed to organs and tissues of the body. Acetone can also be absorbed dermally. Acetone is metabolized mainly in the liver by three separate gluconeogenic pathways, leading to the production of glucose with subsequent liberation of carbon dioxide. With the possible exception of formate, none of the intermediate metabolites appear to be toxic. Acetone and acetone-derived carbon dioxide are excreted mainly in the expired breath, with very little acetone excreted in the urine. Elimination of acetone is generally complete within l-3 days, depending on the dose and duration of exposure, and has little tendency to accumulate. Acetone is also produced endogenously in the body during lipid metabolism, which increases with fasting. Normal levels of acetone in breath, blood, and urine can vary widely depending on a number of factors, such as infancy, pregnancy, lactation, diabetes, physical exercise, dieting, physical trauma, and alcohol consumption.

As a solvent, acetone is irritating to mucous membranes, and exposure to the vapors can irritate the respiratory system and eyes. Acetone has anesthetic properties and causes headaches, lightheadedness, confusion, dizziness, and can lead to unconsciousness and coma in humans at high enough exposure levels. Neurobehavioral effects have been observed in humans exposed acutely by inhalation either in the workplace or in laboratory experiments. Hematological effects, which might indicate immunological effects, have been observed in humans exposed acutely to acetone in laboratory experiments. Acute inhalation of acetone may shorten the menstrual cycle. Exposure to acetone vapor can also lead to increased pulse rates, gastrointestinal irritation, nausea, vomiting, and hemorrhage. However, the odor threshold of acetone (l00-140 ppm) and the feelings of irritancy are excellent warning properties that generally preclude serious inhalation over-exposure. Accidental or intentional ingestion of acetone can cause erosions in the mouth, coma, and diabetes-like symptoms. Acute dermal exposure of humans to liquid acetone resulted in degenerative changes in the epidermis, and a case of contact dermatitis was reported.

Acetone is also irritating to the respiratory system of animals and produces narcosis, coma, and behavioral effects upon acute inhalation exposure. Hematological effects have also been observed in animals. Acute inhalation exposure of animals during gestation has resulted in decreased fetal body weight and increased incidences of late resorption and reduced ossification. Acute oral exposure of animals resulted in enzyme induction in the respiratory system, bone marrow, gastrointestinal tract, kidney, and liver, increased liver weight and bone marrow hypoplasia, degeneration of apical microvilli in renal tubules, and reduced insulin-stimulated glucose oxidation in adipose tissue. Acute oral exposure of animals also resulted in neurological effects, such as languid behavior, prostration before death, reproductive effects (reduced reproduction index and increased duration of gestation), and developmental effects (reduced postnatal pup survival and reduced fetal weight). Intermediate-duration oral studies in animals have found liver effects, hematological effects, nephropathy, and effects on male reproductive organs. Ocular exposure to undiluted or concentrated acetone has produced severe cornea1 burns and necrosis, and dermal exposure of animals to acetone has resulted in reports of cataracts in one species and only a single report of amyloidosis. These observations have not been made by other investigators or in other species, despite many experiments involving dermal exposure of test animals to acetone.

The relevance of the liver, reproductive, and developmental effects to humans is not known, since these end points have not been sufficiently examined in humans. However, few species differences exist in the toxicokinetics of acetone, suggesting that these effects might be of concern for humans. The renal effects may be specific for male rats, and the cataract formation may be specific for guinea pigs, The relevance of amyloidosis in completely unknown. Acetone appears to have no delayed toxic effects. Acetone may be weakly genotoxic, but the majority of genotoxicity assays were negative. Acetone has not been studied for carcinogenicity by the inhalation or oral route, but it was not tumorigenic when tested alone, when tested as a tumor initiator, or when tested as a tumor promoter in skin painting studies.

One of the most studied effects of acetone is the induction of microsomal enzymes, particularly of cytochrome P-450IIEl. Acetone induces its own metabolism by this induction, and potentiates the toxicity of numerous other chemicals by enhancing the metabolism, which depends on cytochrome P-450IIE1, to reactive intermediates. The induction of cytochrome P-45011El by acetone has been documented in many species, and therefore poses a concern for humans exposed to acetone and the chemicals whose toxicity is potentiated by acetone.

Based on results of animal studies, which indicate that male animals are more susceptible than female animals, men may be more susceptible than women to the hematological, hepatic, and renal effects, and effects on reproductive organs. Furthermore, acetone may exacerbate preexisting hematological, liver, kidney, or reproductive disorders in humans. The very young and the elderly may be more susceptible. Fasting and diabetes increases endogenous levels of acetone in humans, suggesting that dieters and diabetics may have a higher body burden, and additional exposure to acetone may make them more susceptible to any effects. Results in animals suggest that the rate of acetone metabolism is slower in pregnancy, making pregnant animals more susceptible, and this susceptibility might apply to humans.

The general population can be exposed to acetone in the air, in contaminated water and soil, and by ingestion of food containing acetone. As discussed in chapter 5, acetone is emitted into the air from plants and trees, volcanic eruptions, forest fires, automobile exhaust, chemical manufacturing, tobacco smoke, wood burning and pulp, refuse in polyethylene combustion, petroleum storage facilities, landfill sites, and solvent use. Acetone is also found in nail polish remover, paint remover, glue, and cleaning agents. Acetone is released into water by chemical manufacturing industries and energy-related industries. Acetone can be released to soil from municipal and industrial landfills, from atmospheric deposition, from disposed agricultural, food and animals wastes, and from household septic tanks. The half-life of acetone in air due to reactions with hydroxyl radical and photolysis is 22 days. The relatively long half-life permits transport to areas remote from the source. Because of its high water solubility, precipitation can remove acetone from the air to surface water and soil. In water and soil acetone undergoes microbial degradation but can also evaporate back into the atmosphere, depending on the moisture content of soil. Adsorption to soil and sediment is inconsequential. Acetone does not accumulate in fish or other aquatic or terrestrial organisms. Ambient air levels of acetone average $\leq$l ppb (v/v) in remote areas, 3 ppb in rural areas, 6.9 ppb in urban air, and 8 ppb in indoor air due to the use of household consumer products. Acetone levels can be $\leq$30 ppb in seawater, $\leq$40 ppb in river water, $\leq$62 ppm in industrial landfill leachate, 0.3-3,000 ppb in well water, and $\leq$1 ppb in finished drinking water. Occupations in which workers may be exposed to higher levels of acetone include paint manufacturing, plastics manufacturing, artificial fiber industries, shoe factories, professional painting, and commercial cleaning. The OSHA standard for a time-weighted average exposure to acetone over an 8-hour workday and 40-hour workweek is 750 ppm, and the short-term exposure limit is 1,000 ppm.

Minimal Risk Levels for Acetone

Inhalation MRLs

- An MRL of 26 ppm has been derived for acute-duration inhalation exposure (14 days or less) to acetone.

The MRL was based on a LOAEL of 237 ppm for 4 hours for neurobehavioral effects in an experimental study in humans (Dick et al. 1989). In this study, groups of 11 men and 11 women were exposed for 4 hours to acetone at a concentration of 237 ppm. Statistically significant changes in performance from controls were seen in two measures of auditory tone discrimination (increased response time and increased false alarms) and in anger and hostility. Neurological and behavioral effects have also been observed in humans exposed to 250 ppm acetone for 6 hours or repeatedly for 6 hours/day for 6 days (Matsushita et al. 1969a, 1969b). Effects included lack of energy, general weakness, delayed visual reaction time, and headache. Although irritation of the nose, throat, and trachea was reported in humans exposed to 100 ppm for 6 hours (Matsushita et al. 1969b), other studies in humans report respiratory irritation only at higher levels (≥250 ppm) for longer durations (Matsushita et al. 1969a; Nelson et al. 1943; Raleigh and McGee 1972; Ross 1983). Furthermore, the reporting of these irritating effects was subjective, and only six volunteers were exposed to 100 ppm.

- An MRL of 13 ppm has been derived for intermediate-duration inhalation exposure (15-364 days) to acetone.

The MRL was based on a LOAEL of 1,250 ppm for neurological effects in volunteers in a 6-week study (Stewart et al. 1975). There was a statistically significant increase in amplitude of the visual evoked response in subjects tested following exposure to 1,250 ppm. Neurological and behavioral effects (lack of energy, general weakness, delayed visual reaction time, and headache) have also been observed in humans exposed to 250 ppm acetone for 5.25 hours or repeatedly for 6 hours/day for 6 days (Matsushita et al. 1969a, 1969b). Increased anger and hostility, as well as increased response time and rate of false negatives in a test of auditory tone discrimination, were reported in volunteers exposed to 237 ppm for 4 hours (Dick et al. 1989). No other effects were detected in humans or animals exposed to acetone for intermediate durations (Bruckner and Peterson 1981b; Stewart et al. 1975)

- An MRL of 13 ppm has been derived for chronic-duration inhalation exposure (365 days or more) to acetone.

The MRL was based on a LOAEL of 1,250 ppm for neurological effects in volunteers in a 6-week study (Stewart et al. 1975). There was a statistically significant increase in amplitude of the visual evoked response in subjects tested following exposure to 1,250 ppm. Neurological and behavioral effects (lack of energy, general weakness, delayed visual reaction time, and headache) have also been observed in humans exposed to 250 ppm acetone for 5.25 hours or repeatedly for 6 hours/day for 6 days (Matsushita et al. 1969a, 1969b). Increased anger and hostility, as well as increased response time and rate of false negatives in a test of auditory tone discrimination, were reported in volunteers exposed to 237 ppm for 4 hours (Dick et al. 1989). A health survey of workers exposed to acetone between 3 months and 23 years revealed no systemic effects (Ott et al. 1983a, 1983c).

Oral MRLs

- An MRL of 2 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to acetone.

The MRL was based on a NOAEL of 200 mg/kg/day for macrocytic anemia in rats treated with acetone in the drinking water for 13 weeks (Dietz et al. 1991; NTP 1991). The LOAEL was 400 mg/kg/day. Hematological effects have been observed in humans exposed by inhalation to acetone (Matsushita et al. 1969a, 1969b), in rats exposed to 6,942 mg/kg/day in the drinking water for 14 days (Dietz et al. 1991; NTP 1991), and in rats treated by gavage with 2,500 mg/kg/day for 93-95 days (American Biogenics Corp. 1986). Male rats treated with 900 mg/kg/day in the drinking water also had increased incidence of age-related nephropathy, which increased in severity as the dose increased (Dietz et al. 1991; NTP 1991). These renal lesions were not seen in female rats or in male or female mice similarly treated. In male rats treated by gavage with $\geq$500 mg/kg/day, but not 100 mg/kg/day, an enhancement of age-related nephropathy, accompanied by hyaline droplet accumulation, was observed (American Biogenics Corp. 1986). Female rats had enhanced age-related nephropathy only at the highest dose (2,500 mg/kg/day), but no evidence of hyaline droplet accumulation was found. Because the mechanism for acetone-induced renal toxicity has not been

elucidated, but may be specific for male rats, renal end points have not been considered for the derivation of MRLs for acetone.

An MRL has not been derived for acute-duration oral exposure (14 days or less) to acetone because a suitable NOAEL or LOAEL for a sensitive end point has not been sufficiently characterized, Such effects as bone marrow hypoplasia, reduced insulin-stimulated glucose oxidation, and hepatocellular hypertrophy were observed in rats or mice exposed to acetone in the drinking water for acute durations (Dietz et al. 1991; NTP 1991; Skutches et al. 1990), but the NOAEL and LOAEL values for these effects are close to or fall within the range of LD_{50} values for rats administered acetone by gavage (Freeman and Hayes 1985; Kimura et al. 1971). Degeneration of apical microvilli in renal tubules was observed in male rats treated once by gavage with 871 mg/kg (Brown and Hewitt 1984), but incidences were not reported. Furthermore, as discussed above, acetone-induced renal lesions may be specific for male rats and may not represent a suitable end point to consider for MRL derivation for acetone.

An MRL was not derived for chronic-duration oral exposure (365 days or more) to acetone because no chronic-duration studies were located.

Death. No studies were located regarding death of humans after dermal exposure to acetone. A retrospective mortality study of workers exposed to time-weighted-average acetone concentrations of 380-1,070 ppm at a cellulose fiber plant where acetone was used as the only solvent found no significant excess risk of death from any cause compared with rates for the U.S. general population (Ott et al. 1983a, 1983b). Furthermore, in the 1991 Annual Report of the American Association of Poison Control Centers National Data Collection System, no fatalities were reported among 1,124 cases of accidental or intentional ingestion of acetone (Litovitz et al. 1992). However, inhalation of saturated atmospheres of acetone or accidental or intentional ingestion of acetone can lead to unconsciousness if doses are sufficiently high, and death could ensue if the subjects do not receive medical intervention. Two workers became unconscious after a single accidental exposure to acetone at high concentrations (>1,200 ppm) (Ross 1973). Coma developed in patients who had hip casts applied with acetone present in the setting fluid (Chatterton and Elliott 1946; Fitzpatrick and Claire 1947; Harris and Jackson 1952; Renshaw and Mitchell 1956; Strong 1944). These patients were exposed to acetone by inhalation during the application and from evaporation of acetone from the casts after application, but dermal exposure also could have occurred. In most cases of accidental or

intentional ingestion, the quantity of acetone consumed is not known. In one case, a man became comatose after ingesting 100 mL of liquid cement containing 15% polyvinyl chloride, 18% acetone, 28% 2-butanone, and 39% cyclohexanone, along with 750 mL sake (Sakata et al. 1989). The dose of acetone ingested would be approximately 231 mg/kg, but the other components in the cement and the sake could have contributed to his condition. In another case, a man became comatose after ingesting 200 mL of pure acetone (2,241 mg/kg) (Gitelson et al. 1966). Since the patients received medical treatment, none died.

High concentrations of acetone in air are required to produce death in animals. An 8-hour LC_{50} value of 21,091 ppm and a 4-hour LC_{50} value of 31,944 ppm were found for female rats (Pozzani et al. 1959). Death of animals has occurred after acute inhalation exposure to l0,000-50,000 ppm (Bruckner and Peterson 1981b; Smyth et al. 1962; Specht et al. 1939). No information was located regarding levels of acetone that would result in death of animals after inhalation exposure for longer durations. Acute oral LD_{50} values in rats have ranged from 1,726 to 9,833 mg/kg, depending on age and strain (Freeman and Hayes 1985; Kimura et al. 1971; Pozzani et al. 1959; Smyth et al, 1962). In general, newborn rats are the most sensitive, followed by 14-day-old rats, older adult rats, and younger adult rats (Kimura et al. 1971), and Sprague-Dawley rats (Freeman and Hayes 1985; Kimura et al. 1971) appeared to be more sensitive than Wistar rats (Smyth et al. 1962) or Nelson rats (Pozzani et al. 1959). Acute oral LD_{50} values of 5,250 mg/kg for male mice (Tanii et al. 1986) and 3,687 mg/kg for guinea pigs (Striegel and Carpenter 1961) have been reported. Doses of 3,922-7,844 mg/kg (Walton et al. 1928) and 7,500-8,000 mg/kg (Albertoni 1884) have been reported to be fatal to rabbits and puppies, respectively. An acute oral dose of 2,400 mg/kg was fatal to one of four pregnant mice, and more pregnant mice died at higher doses (EHRT 1987), but no effect on mortality was found in nonpregnant mice exposed to acetone in drinking water at doses $\leq$ 1,298 mg/kg/day for 13 weeks (NTP 1991). Therefore, pregnant mice may be more susceptible than nonpregnant mice. Likewise, in intermediate-duration studies, no effects on mortality were found in rats exposed to acetone by gavage (American Biogenics Corp. 1986) or in drinking water (NTP 1991) at doses $\leq$3,400 mg/kg/day. In studies attempting to determine dermal LD_{50} values for animals, the highest doses used did not result in death. Therefore, the LD_{50} values for dermal exposure were >9.4 mL/kg for guinea pigs (Roudabush et al. 1965) and >20 mL/kg for rabbits (Smyth et al. 1962).

The lethality of acetone is related to its narcotic properties, since prostration and unconsciousness usually precede death (Albertoni 1984; EHRT 1987; Freeman and Hayes 1985; Specht et al. 1939;

Walton et al. 1928). It is unlikely that humans would die after exposure to acetone at ambient air, soil, or water levels, or at levels present at hazardous waste sites. Accidental occupational exposure and accidental or intentional ingestion of acetone could conceivably lead to death if the victims do not receive medical attention. In the case of the worker who became unconscious at an acetone level of 900 ppm, the OSHA standard of 750 ppm (OSHA 1989) was exceeded.

Systemic Effects

Respiratory Effects. Acetone does not appear to produce respiratory effects in humans or animals after oral or dermal exposure. As is common with solvent exposure, the respiratory effects of acetone observed in humans exposed by inhalation are related to the irritating properties of acetone. Experimental subjects experienced irritation of the nose, throat, and trachea at acute inhalation concentrations ≥100 ppm for 6 hours (Matsushita et al. 1969b), but this appears to be related to the duration of exposure, as people exposed to 200 ppm for 3-5 minutes experienced no irritation and estimated that they could tolerate this concentration for 8 hours (Nelson et al. 1943). Workers exposed to higher concentrations also complained of nose, throat, and lung irritation (Raleigh and McGee 1972; Ross 1973). Individual sensitivity to acetone-induced respiratory irritation appears to be highly variable (Nelson et al. 1943). Pulmonary function testing of volunteers exposed to ≤1,250 ppm acetone intermittently for various durations in a complex protocol revealed no abnormalities caused by the exposure (Stewart et al. 1975).

Acetone is also irritating to the respiratory system of animals after acute inhalation exposure. Guinea pigs that died after exposure to high concentrations of acetone had pulmonary congestion and edema due to the irritating properties of acetone, and hemorrhage of the lung, probably as a consequence of death (Specht et al. 1939). An RC_{50} of 77,516 ppm was found for mice (Kane et al. 1980). The decrease in respiratory rate is due to sensory irritation and is typical of sensory irritants, No intermediate-duration inhalation studies examined animals for respiratory effects, and no chronic-duration inhalation studies in animals were located. Changes in respiratory rates or irregular respiration were observed in rabbits dosed orally with ≥3,922 mg/kg (Walton et al. 1928) and dogs dosed orally with 4,000 mg/kg (Albertoni 1884), but were accompanied by signs of narcosis. Acute oral exposure of rabbits to 863 mg/kg/day resulted in the induction of microsomal enzymes in the nasal mucosa (Ding and Coon 1990), but induction of microsomal enzymes is a normal physiological response to xenobiotics and is not adverse. However, acetone potentiates the toxicity of chemicals by

enzyme induction (see Section 2.6). While it is conceivable that acetone might potentiate the toxicity of chemicals toxic to the respiratory system, no such interactions were located.

It is unlikely that people would experience respiratory irritation after exposure to acetone at ambient air, soil, or water levels, or at levels present at hazardous waste sites. Occupational exposure to acetone can cause respiratory irritation, but other respiratory effects are unlikely. The OSHA time-weighted average standard to protect against irritation is 750 ppm, and the short-term exposure limit is 1,000 ppm (OSHA 1989), which is higher than the exposure levels producing irritation in laboratory subjects.

Cardiovascular Effects. No studies of workers located reported cardiovascular effects of acetone unrelated to narcosis. A retrospective mortality study of workers exposed to time-weighted-average acetone concentrations of 380-1,070 ppm at a cellulose fiber plant where acetone was used as the only solvent found no significant excess risk of death from circulatory system disease or ischemic heart disease compared with rates for the U.S. general population (Ott et al. 1983a, 1983b). Electrocardiography of volunteers exposed to $\leq$1,250 ppm acetone intermittently for various durations in a complex protocol revealed no abnormalities caused by the exposure (Stewart et al. 1975). Patients exposed to acetone by inhalation and/or dermally after application of casts for which acetone was used in the setting solution commonly had high pulse rates (120-l60/minute) (Chatterton and Elliott 1946; Hift and Pate1 1961; Pomerantz 1950; Renshaw and Mitchell 1956). No gross heart lesions were found in guinea pigs exposed acutely by inhalation to lethal concentrations (Specht et al. 1939), and no histopathological heart lesions were found in rats exposed by inhalation to acetone for 2-8 weeks (Bruckner and Peterson I981b) or in rats or mice exposed orally in intermediate-duration studies (American Biogenics Corp. 1986; NTP 1991). However, amyloidosis was observed in the hearts of mice whose lumbo-sacral regions were painted twice weekly with an unspecified quantity of acetone for 12 months (Barr-Nea and Wolman 1977). The significance of the amyloidogenic effect of acetone to humans is unknown since no clinical data regarding amyloidosis in humans who come in frequent dermal contact with acetone, such as manicurists, are available.

The effects of acetone on the perfused isolated hearts of rabbits (Raje 1980) and the isolated right atrium of rats (Chentanez et al. 1987) have been investigated *in vitro.* Acetone at concentrations of 0.5 and 1.0% (v/v) in the perfusate inhibited the force of cardiac contractions and increased the heart rate of rabbits in a dose-related manner (Raje 1980). Acetone also increased the coronary flow, but

not in a dose-related manner. The author stated, however, that the concentrations of acetone were physiologically unrealistic. Acetone at concentrations of l0-210 mM in the bathing solution increased the atria1 contraction rate of the isolated rat atrium in a dose-dependent manner (Chentanez et al. 1987). At concentrations >210 mM, the atria1 contraction rate gradually decreased to the normal control value. At concentrations of l0-750 mM, acetone resulted in a dose-dependent increase in the release of norepinephrine from the right atrium. The dose-response curves for atria1 contraction and peak norepinephrine release were parallel at acetone concentrations of l0-210 mM, but norepinephrine release still increased at concentrations ≤500 mM, while the atria1 contraction rate decreased at ≥210 mM. The results indicated that the increase in atria1 contraction rate may be due in part to an increase in norepinephrine release from the atria1 sympathetic nerve terminals at the lower concentrations, but the higher concentrations may have been too toxic for norepinephrine to exert a further effect on atria1 contraction. These *in vitro* studies were conducted to investigate the mechanism of tachycardia in glue-sniffers to determine whether acetone, one of the components of glue, was the component responsible for the tachycardia. Other components of glue, however, could also cause tachycardia. These *in vitro* experiments suggest that acetone may cause tachycardia *in vivo*, but tachycardia was not demonstrated by electrocardiography in the subjects exposed to ≤1,250 ppm in the experiments by Stewart et al. (1975), and rapid heart rates were not reported as one of the subjective symptoms in workers or experimental subjects.

The weight of evidence for cardiovascular effects in humans and animals exposed to acetone *in vivo* suggest that it is unlikely that people would experience cardiovascular effects after exposure to acetone at ambient air, soil, or water levels, or at levels present at hazardous waste sites.

Gastrointestinal Effects. Nausea and vomiting of blood have been observed in patients who had hip casts applied with acetone present in the setting fluid (Chatterton and Elliott 1946; Fitzpatrick and Claire 1947; Harris and Jackson 1952; Hift and Pate1 1961; Pomerantz 1950; Renshaw and Mitchell 1956; Strong 1944). The vomitus contained blood several hours after the onset of vomiting; therefore, the gastrointestinal hemorrhage may have been due to trauma of repeated vomiting. These patients were exposed to acetone by inhalation during the application and from evaporation of acetone from the casts after application, but dermal exposure also could have occurred. None of the workers examined in on-site medical evaluations (Raleigh and McGee 1972) or experimental subjects exposed to ≤1,250 ppm complained of nausea or vomiting (DiVincenzo et al. 1973; Matsushita et al. 1969a, 1969b; Stewart et al. 1975). However, complaints of nausea and intermittent vomiting were reported

by workers with accidental exposure to acetone (>12,000 ppm) (Ross 1973). It is possible that nausea and vomiting are secondary to central nervous system toxicity. Effects on the stomach or intestines were not reported in case reports of people who ingested acetone intentionally or accidentally (Gamis and Wasserman 1988; Gitelson et al. 1966; Sakata et al. 1989), but a man who intentionally drank ≈200 mL of pure acetone (≈2,241 mg/kg) had a red and swollen throat and erosions in the soft palate and entrance to the esophagus (Gitelson et al. 1966).

No gross stomach lesions were found in guinea pigs exposed acutely by inhalation to lethal concentrations (Specht et al. 1939), and no histopathological stomach or intestinal lesions were found in rats or mice exposed orally in intermediate-duration studies (American Biogenics Corp. 1986; NTP 1991). Although cytochrome P-450 enzyme levels were significantly elevated in duodenal and jejunal microsomes from rats exposed to acetone in drinking water for 3 days (Carriere et al. 1992), induction of microsomal enzymes is not considered an adverse effect.

People exposed to acetone at work could experience nausea and vomiting, but levels of acetone in ambient air, soil, or water at hazardous waste sites are not likely to be high enough to cause nausea and vomiting.

Hematological Effects. Acetone exposure has caused hematological effects in both humans and animals. In men exposed experimentally to ≥500 ppm acetone for 6 hours or for 6 hours/day for 6 days, significantly increased white blood cell counts, increased eosinophil counts, and decreased phagocytic activity of neutrophils were observed, compared with controls (Matsushita et al. 1969a, 1969b). No women were included in these studies. However, experimental studies that examined hematological indices did not find any abnormalities in men (women not included in study) at exposure levels of 500 ppm for 2 hours (DiVincenzo et al. 1973) or in men or women at exposure levels ≤1,250 ppm acetone for ≤7.5 hours for various durations (Stewart et al. 1975). The reasons for these different results are not known. In a health evaluation survey of 245 workers exposed to time-weighted- average acetone concentrations of 380-1,070 ppm at a cellulose fiber production plant where acetone was used as the only solvent, all hematological parameters were within normal limits (Ott et al. 1983a, 1983c).

Oral exposure of rats to acetone was found to significantly increase the level of cytochrome P-45IIE1 in bone marrow microsomes (Schnier et al. 1989). While microsomal enzyme induction is not

generally considered an adverse effect, the hemotoxicity of benzene depends upon its activation by cytochrome P-450IIEl (see Section 2.6); therefore, acetone may potentiate the hemotoxicity of benzene by this mechanism.

Hematological effects observed in animals consisted of bone marrow hypoplasia in male rats, but not female rats, exposed to acetone in the drinking water for 14 days at 6,942 mg/kg/day (NTP 1991); evidence of macrocytic anemia in male rats at ≥400 mg/kg/day and nonspecific hematological effects not indicative of anemia in female rats at 3,100 mg/kg/day via drinking water for 13 weeks (NTP 1991); increased hemoglobin, hematocrit, and mean cell volume in male rats, but not female rats, treated by gavage at 2,500 mg/kg/day for 46 days, and in both males and females at this dose for 13 weeks (American Biogenics Corp. 1986). In mice treated at ≤12,725 mg/kg/day for 14 days, it was not clear whether bone marrow was examined, but in the 13-week study, no hematological effects or histologically observable lesions in hematopoietic tissues were found in mice (NTP 1991). Thus, sex differences exist in the hematological effects of acetone in animals, and species differences exist in the hematological effects of acetone among animals and between animals and humans.

The weight of evidence indicates that acetone exposure might produce hematological effects in humans. Based on animals studies, men might be more susceptible than women. Whether levels of acetone in ambient air, soil, or water, or levels present at hazardous waste sites are high enough to cause hematological effects is not known, but occupational exposure levels may be high enough, as the OSHA time-weighted average standard is 750 ppm and the short-term exposure limit is 1,000 ppm (OSHA 1989).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation, oral, or dermal exposure in humans or animals after inhalation or dermal exposure to acetone. Histological examination of rats and mice in intermediate-duration drinking water or gavage studies did not find any evidence of musculoskeletal effects (American Biogenics Corp. 1986; NTP 1991)

In appears unlikely that exposure of humans to acetone in any setting would result in musculoskeletal effects.

Hepatic Effects. No indication that acetone caused hepatic effects in humans was found in controlled studies of volunteers based on analysis of clinical chemistry parameters (DiVincenzo et al. 1973; Stewart et al. 1975). Furthermore, none of the located studies of workers or case reports documented hepatic effects. In a health evaluation survey of 245 workers exposed to time-weighted-average acetone concentrations of 380-1,070 ppm at a cellulose fiber production plant where acetone was used as the only solvent, all clinical blood chemistry parameters (aspartate aminotransferase, alanine aminotransferase, lactic dehydrogenase, alkaline phosphatase, total bilirubin, and albumin) were within normal limits (Ott et al. 1983a, 1983c).

Inhalation and oral studies in animals have found only mild to moderate hepatic effects. Guinea pigs acutely exposed by inhalation to lethal concentrations had fatty deposits in the liver, which were considered toxicologically insignificant (Specht et al. 1939). Mice exposed intermittently to 6,600 ppm acetone during gestation had significantly increased absolute and relative liver weights, indicative of maternal toxicity (NTP 1988). The increased liver weight could have been associated with enzyme induction. No increases in serum levels of hepatic enzymes indicative of liver injury were found in acute oral studies in rats (Brown and Hewitt 1984; Charhonneau et al. 1986b; Plaa *et* al. 1982), and no histopathological liver lesions were found in an acute oral study in mice (Jeffery et al. 1991). Liver effects observed in animals orally exposed to acetone consisted of dose-related increased liver weight in mice exposed to acetone in drinking water at ≥965 mg/kg/day and hepatocellular hypertrophy at ≥3,896 mg/kg/day for 14 days, probably associated with microsomal enzyme induction (NTP 1991); significantly increased levels of serum alanine aminotransferase in male rats, but not female rats, at a gavage dose of 2,500 mg/kg/day for 46 days or 13 weeks, and significantly increased liver weights in female rats at ≥500 mg/kg/day and in male rats at 2,500 mg/kg/day for 13 weeks (American Biogenics Corp. 1986); and significantly increased liver weights in both sexes of rats at the same drinking water concentration (1,600 mg/kg/day for females, 1,700 mg/kg/day for males) and in female mice, but not male mice, at 11,298 mg/kg/day for 13 weeks (NTP 1991). Histological examination of the liver of rats and mice in the 13-week studies revealed no evidence of liver pathology (American Biogenics Corp. 1986; NTP 1991). The increased liver weight in mice in the 13-week study was not associated with hepatocellular hypertrophy as was seen in the 14-day study, suggesting a development of tolerance (NTP 1991). In the absence of histologically observable liver lesions in rats in the 13-week gavage study (American Biogenics Corp. 1986), the toxicological significance of the increased serum level of alanine aminotransferase in the same study is questionable. Amyloidosis was observed in the livers of mice whose lumbo-sacral regions were painted twice

weekly with an unspecified quantity of acetone for 12 months (Barr-Nea and Wolman 1977). The significance of the amyloidogenic effect of acetone to humans is unknown, since no clinical data regarding amyloidosis in humans who come in frequent dermal contact with acetone, such as manicurists, are available.

As mentioned above, increased liver weight was probably associated with hepatic microsomal enzyme induction. Numerous acute oral and inhalation studies have demonstrated that acetone induces hepatic microsomal monooxygenase activities, particularly activities associated with cytochrome P-450IIEl (see Sections 2.2.1.2 and 2.2.2.2). Acetone potentiates the hepatotoxicity of carbon tetrachloride and chloroform and other chemicals (see Section 2.6) by inducing microsomal enzymes that metabolize these chemicals to reactive intermediates (see Sections 2.3.5 and 2.6).

Therefore, it is likely that people would develop no or only minimal liver effects by exposure to acetone alone at ambient air, soil, or water levels, at levels present at hazardous waste sites, or in occupational settings. However, exposure to acetone alone is extremely unlikely in these scenarios, since many other chemicals are also present in air, soil, and water and at hazardous waste sites, and workers are commonly exposed to other solvents and chemicals that produce hepatotoxic effects potentiated by acetone. Such coexposure might make people more susceptible to the hepatotoxicity of these chemicals.

Renal Effects. No indication that acetone caused renal effects in humans was found in controlled studies of volunteers based on analysis of clinical chemistry parameters (blood urea nitrogen, uric acid) and urinalysis (DiVincenzo et al. 1973; Stewart et al. 1975). Furthermore, none of the located studies of workers or case reports documented renal effects.

The only indication that inhalation exposure to acetone causes renal effects in animals was the consistent finding of congestion or distention of renal tubules or glomeruli in guinea pigs exposed acutely to lethal levels of acetone (Specht et al. 1939). Rats exposed intermittently to 19,000 ppm for 18 weeks had no clinical or histological evidence of kidney damage (Bruckner and Peterson 1981b). Amyloidosis was observed in the kidneys of mice whose lumbo-sacral regions were painted twice weekly with an unspecified quantity of acetone for 12 months (Barr-Nea and Wolman 1977). The significance of the amyloidogenic effect of acetone to humans is unknown, since no clinical data

regarding amyloidosis in humans who come in frequent dermal contact with acetone, such as manicurists, are available.

No significant differences in kidney weight, BUN levels, or organic ion accumulation by renal slices were found in rats given 1,766 mg/kg/day acetone for 2 days compared with controls (Valentovic et al. 1992). Oral exposure of animals to acetone in other studies, however, has resulted in adverse renal effects, including degeneration of the apical microvilli of renal tubules in rats given a single oral dose of 871 mg/kg (Brown and Hewitt 1984); dose-related increased kidney weight in mice at ≥6,348 mg/kg/day in drinking water for 14 days (NTP 1991); increased kidney weight in female rats at ≥1,600 mg/kg/day and in male rats at 3,400 mg/kg/day, and a dose-related increased incidence and/or severity of nephropathy at ≥900 mg/kg/day in male rats, but not female rats, in drinking water for 13 weeks (NTP 1991); and increased kidney weight in female rats at 2500 mg/kg/day and in male rats at 2,500 mg/kg/day by gavage for 13 weeks (American Biogenics Corp. 1986). In addition, increased severity of renal proximal tubule degeneration and intracytoplasmic droplets of granules (hyaline droplets) in the proximal tubular epithelium showed a dose-related increase in males at ≥500 mg/kg/day and in females at 2,500 mg/kg/day (American Biogenics Corp. 1986). The kidney lesions seen in both the drinking water study and the gavage study may indicate that acetone enhanced the age-related nephropathy in rats. No kidney effects were observed in mice given acetone in the drinking water for 13 weeks (NTP 1991). Formate, one of the metabolites of acetone, may be responsible for the nephrotoxicity of acetone (NTP 1991).

Thus, species differences exist in susceptibility to acetone-induced kidney effects. Sex difference also exist; kidney weight increases in female rats at lower doses than in male rats, while histopathological lesions occur in male rats at lower doses than in females.

As in the liver, acetone also induced enzymes in microsomes prepared from kidneys of rats (Hong et al. 1987) and hamsters treated orally with acetone (Menicagli et al. 1990; Ueng et al. 1991). The increased kidney weights observed in rats and mice might also be associated with an increased amount of protein as a result of enzyme induction. Furthermore, acetone might potentiate the nephrotoxicity of other chemicals, such as chloroform, by increasing the rate of metabolism to reactive intermediate via enzyme induction (see Sections 2.3.5 and 2.6).

Since there is no indication that acetone causes kidney effects in humans or animals exposed by inhalation to nonlethal concentrations, exposure of people to acetone alone in ambient air, in air near hazardous waste sites, or at work sites probably poses little risk for the development of nephropathy. Whether levels in water or soil are high enough to increase kidney weight or cause other kidney effects is not known. The relevance of the acetone-enhanced age-related nephropathy seen in male rats treated orally with acetone (American Biogenics Corp. 1986; NTP 1991) to humans is not clear. The kidney lesions were seen in male rats, but not female rats or mice of either sex, in the NTP (1991) study. In the American Biogenics Corp. (1986) study, an increased severity of renal lesions was seen in female rats at the highest dose, but the increased severity was dose-related in male rats at lower doses and was associated with hyaline droplet formation. Hyaline droplet formation was not observed in the NTP (1991) study. The presence of hyaline droplets suggests that the renal effects observed in male rats may be associated with $\alpha_{2\mu}$-globulin syndrome, which appears to be specific for male rats, as this protein has not been found in female rats, mice, or humans (EPA 1991a). This low molecular weight protein has been implicated in the mechanism of chemically-induced renal toxicity and renal tumor formation in male rats for a number of chemicals. Thus, the renal pathology induced in male rats by acetone exposure may have no relevance to human health. The ability of acetone to induce microsomal enzymes may also pose a concern. Exposure to acetone alone is extremely unlikely in these scenarios, since many other chemicals are also present in air, soil, and water and at hazardous waste sites, and workers could be exposed to other chemicals with nephrotoxic effects that are potentiated by acetone. Such coexposure could make people more susceptible to the nephrotoxicity of these chemicals.

Dermal/Ocular Effects. Like many solvents, acetone is irritating to the skin and eyes. Dermal contact with vapors of acetone in air has not been reported to cause dermal effects in humans or animals. No studies were located regarding dermal or ocular effects in humans after oral exposure to acetone. Exposure of humans by direct contact of the skin with liquid acetone for 30 or 90 minutes has resulted in histological and ultrastructural degenerative changes in the epidermis (Lupulescu and Birmingham 1975, 1976; Lupulescu et al. 1972, 1973), and frequent dermal contact may cause contact dermatitis in sensitized humans (Tosti et al. 1988).

Oral exposure of animals to acetone in intermediate-duration studies did not cause any histological changes in the skin (NTP 1991), but dermal exposure of mice resulted in increased DNA synthesis, indicative of irritation (Iversen et al. 19SS), moderate hyperplasia of the epidermis (Iversen et al.

1981), hyperplasia, dermatitis, and hyperkeratosis (DePass et al. 1989); and amyloidosis in the skin (Barr-Nea and Wolman 1977). Hairless guinea pigs developed only mild erythema after direct application of acetone to the dorsal thorax (Taylor et al. 1993).

Like many solvents, acetone is irritating to the eyes. Humans exposed to acetone vapors in the air, either occupationally or in experimental studies, frequently complained of eye irritation (Matsushita et al. 1969a, 1969b; Nelson et al. 1943; Raleigh and McGee 1972; Ross 1973; Sallee and Sappington 1949). Concentrations of acetone in the air $\geq$100 ppm have been reported as irritating to the eyes of humans (Matsushita et al. 1969a). Eye irritation has also been observed in animals exposed to acetone vapors (Specht et al. 1939), and direct instillation of acetone into the eyes of rabbits has caused reversible cornea1 burns (Bolkova and Cejkova 1983), edema of mucous membranes (Larson et al.1956), severe eye necrosis (Carpenter and Smyth 1946; Smyth et al. 1962), and uveal melanocytic hyperplasia (Pe'er et al. 1992). Ocular effects have been observed in animals even after dermal exposure. Application of acetone to shaved skin of guinea pigs, but not rabbits for 3 or 6 weeks resulted in the development of cataracts (Rengstorff et al. 1972, 1976; Rengstorff and Khafagy 1985). Cataracts also occurred in guinea pigs after subcutaneous injection of acetone (3.8 mg/kg) 3 days/week for 3 weeks (Rengstorff et al. 1972). The difference in response between the guinea pigs and rabbits reflect species differences in susceptibility to the cataractogenic effects of acetone, as twice as much acetone was applied to rabbits than to guinea pigs. However, no cataracts or lens opacities were found in hairless guinea pigs to which acetone was applied to the skin for 6 months (Taylor et al. 1993). Genetic differences in susceptibility between hairless and normal guinea pigs was suggested to account for the different results, but was considered to be unlikely. Acetone produced a dose-related increased incidence of opacity in bovine cornea1 preparations *in vitro* (Gautheron et al. 1992). No cases of cataract formation in humans exposed to acetone by any route were located; therefore, the relevance of these findings to public health is not known. Histological and/or ophthalmoscopic examination of eyes of rats and mice did not reveal any ocular effects in intermediate-duration oral studies (American Biogenics Corp. 1986; NTP 1991).

Eye irritation is a concern for people exposed to acetone vapors occupationally, and splashing of liquid acetone into the eyes may cause cornea1 burns or necrosis, but concentrations of acetone in air in the general environment or near hazardous waste sites are probably not high enough to produce eye irritation. Dermal contact with soil containing high concentrations of acetone could possibly cause some dermal irritation, but acetone in water would probably be too dilute to irritate the buccal cavity.

The relevance of the observed cataract formation and amyloidosis in animals after dermal exposure to acetone to human health is not known.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation or dermal exposure to acetone, but a case report of man who intentionally drank 200 mL pure acetone (2,241 mg/kg) described the subsequent development of diabetes-like symptoms, such as excessive thirst, polyuria, and hyperglycemia (Gitelson et al. 1966). In an acute study, treatment of fasted or fed rats by gavage with 3,214 mg/kg/day significantly reduced insulin-stimulated glucose oxidation in adipose tissue (Skutches et al. 1990). The reduction was greater in fasted rats than in fed rats. Acetone is a ketone so exposure can result in ketosis, and fasting can result in further ketosis through the production of ketone bodies in response to low fat intake. Diabetics with ketoacidosis produce more acetone endogenously than nondiabetic people (Fisher 1951; Reichard et al. 1986; Sulway and Malins 1970); therefore, the fact that exogenous acetone mimics some aspects of a diabetic-like condition is not surprising.

Most of the information regarding other systemic effects in animals after inhalation and oral exposure relates to body weight changes. Pregnant rats that were exposed to acetone by inhalation at 11,000 ppm during gestation had reduced body weights (NTP, 1988), but no effect on body weight of nonpregnant female rats exposed to 16,000 ppm for 2 weeks was found in another study (Goldberg et al., 1964). Furthermore, maternal body weights of mice were statistically significantly reduced on day 3 postpartum after treatment with 3,500 mg/kg/day acetone by gavage during gestation (EHRT 1987). It is possible that the condition of pregnancy made the rats and mice more susceptible to body weight reduction. Although body weight loss was observed in rats treated by gavage with lethal doses of acetone (Freeman and Hayes 1985), no indication of decreased body weight gain unrelated to decreased water consumption was found in animals exposed to acetone in drinking water (Furner et al. 1972; Hetu and Joly 1988; Ladefoged et al. 1989; NTP 1991; Valentovic et al. 1992). The only information on other systemic effects in animals exposed dermally to acetone was the finding of amyloidosis in the adrenals and pancreas of mice (Barr-Nea and Wolman 1977) and a transient weight loss of 60 g over a 2-week period in hairless guinea pigs to which acetone was applied to the skin for 6 months (Taylor et al. 1993). The relevance of these findings to human health is not known.

Exposure to acetone orally or by inhalation may result in ketosis, but whether concentrations of acetone in air, water, or soil in the general environment or at hazardous waste sites would result in

appreciable ketosis is not known. Occupational levels could be high enough to produce ketosis. Based on results of animal studies, pregnant women may be susceptible to body weight reduction if exposed to acetone, but it is unlikely that exposure levels in the environment or near hazardous waste sites would be high enough to cause body weight loss.

Immunological Effects. Information regarding immunological effects in humans after exposure to acetone is limited. Significantly increased white blood cell counts, increased eosinophil counts, and decreased phagocytic activity of neutrophils were found in volunteers exposed to 500 ppm for a single 6-hour exposure or intermittently for 6 days (Matsushita et al. 1969a, 1969b). A case report of a laboratory technician described the development of acute contact dermatitis from handling acetone 2 years after being treated with squaric acid dibutyl ester in acetone for patchy alopecia areata on her scalp (Tosti et al. 1988). This acetone sensitization is considered a rare complication of sensitizing therapies for alopecia areata. No studies were located regarding immunological effects in humans after oral exposure or in animals after inhalation, oral, or dermal exposure to acetone.

While hematological findings in humans may represent immunological effects, they have not been corroborated. Furthermore, other inhalation studies in humans that examined hematological end points did not find any abnormalities (DiVincenzo et al. 1973; Ott et al. 1983a, 1983c; Stewart et al. 1975). The development of contact dermatitis in the laboratory technician appears to be an isolated incident, but it is possible that acetone could produce dermatitis in sensitized humans who come in frequent dermal contact with acetone, such as laboratory workers.

Neurological Effects. No studies were located regarding neurological effects in animals after dermal exposure to acetone, but acetone exposure by the inhalation and oral routes has resulted in neurological effects, related to the narcotic effects of acetone, in both humans and animals. Patients who were exposed to acetone, mainly by inhalation, during and after the application of hip casts with acetone present in the setting fluid became comatose or collapsed (Chatterton and Elliott 1946; Fitzpatrick and Claire 1947; Harris and Jackson 1952; Renshaw and Mitchell 1956; Strong 1944). Some dermal exposure could have contributed to the total exposure. Headache, dizziness, weakness, difficulty speaking, and depression were experienced by a woman after an acetone-containing cast was applied (Pomerantz 1950). In addition, drowsiness, fretfulness, irritability, restlessness, uncoordinated hand movement, and nystagmus developed in patients after application of cast where exposure was considered to be mainly dermal (Hift and Pate1 1961). Neurological effects were commonly

experienced by workers exposed to acetone in the past. These include headache, lightheadedness, dizziness, unsteadiness, confusion, and unconsciousness (Raleigh and McGee 1972; Ross 1973), and have been observed at concentrations of acetone ≥901 ppm in the workplace. Neurobehavioral tests conducted in some of these workers did not reveal any effects of acetone on the parameters examined (Raleigh and McGee et al. 1972). Neurological and behavioral effects, such as, lack of energy and weakness, headache, delayed visual reaction time at 250 ppm for 6 hours or 6 hours/day for 6 days (Matsushita et al. 1969a, 1969b); subjective symptoms of tension, tiredness, and annoyance (Seeber and Kiesswetter 1991; Seeber et al. 1992); increases in response and the percent false negatives in auditory discrimination tests and increases in anger and hostility at 237 ppm for 4 hours (Dick et al. 1989); and increased visual evoked response at 1,250 ppm intermittently in complex protocol (Stewart et al. 1975) have been documented in volunteers tested under controlled laboratory conditions. Electroencephalography revealed no abnormalities (Stewart et al. 1975). In volunteers exposed to 21,049-84,194 ppm acetone for l-8 hours, the time to observation of signs of narcosis, loss of righting reflex, and loss of cornea1 reflex decreased as the exposure concentration increased (Haggard et al. 1944). It should be noted that these concentrations are higher than those resulting in unconsciousness in workers exposed for shorter durations.

Several case reports have described patients in unresponsive, lethargic, or comatose conditions after ingesting acetone (Gamis and Wasserman 1988; Ramu et al. 1978; Sakata et al. 1989), but most of these cases are confounded by coexposure to other possible narcotic agents. The lethargic and comatose conditions of these patients was, however, generally attributed to acetone poisoning. Deep coma developed in a man who intentionally ingested about 200 mL of pure acetone (about 2,241 mg/kg) (Gitelson et al. 1966). Six days after medical treatment, he was ambulatory but had a marked disturbance of gait, which had improved upon follow-up examination 2 months later.

Narcotic effects have been observed in animals acutely exposed to acetone vapors. Signs of narcosis, loss of righting reflex, and loss of cornea1 reflex were observed in rats exposed to concentrations of acetone ≥10,524 ppm (Haggard et al. 1944). Drowsiness, staggering, prostration, clonic movements of hind legs, and deep narcosis were observed in mice exposed to 16,839-84,194 ppm (Mashbitz et al. 1936). The time to observations of these signs decreased as the concentration of acetone increased. Narcosis as evidenced by decreased respiratory and heart rates, paralysis, and coma were observed in guinea pigs exposed to a lethal concentration (21,800 ppm) continuously for periods of 25 minutes ≤24 hours (Specht et al. 1939). The degree of narcosis increased as the exposure duration increased.

Severe narcosis was also observed in mice after a single 6-hour exposure to 11,000 ppm (NTP 1988). Neurobehavioral effects, indicative of narcosis, have been observed in rats (Bruckner and Peterson 1981a; Garcia et al. 1978; Geller et al. 1979b; Goldberg et al. 1964), mice (De Ceaurriz et al. 1984; Glowa and Dews 1987), and baboons (Geller et al. 1979a) acutely exposed to acetone vapors at exposure levels ≥150 ppm for baboons. A statistically significant decrease in absolute brain weight was observed, but no histopathological brain lesions, in rats exposed intermittently to 19,000 ppm in an intermediate-duration study (Bruckner and Peterson 1981a).

Acetone is also neurotoxic in animals after oral exposure. Death in mice and rats exposed acutely was preceded by prostration (EHRT 1987; Freeman and Hayes 1985). Weakness, depression, and unconsciousness were observed in rabbits dosed orally with 3,922-7,844 mg/kg, with the degree and time to onset dependent on dose (Walton et al. 1928). Incoordination, staggering, falling, tremors, delirium, prostration, and coma were observed in dogs and puppies at oral doses of 4,000-8,000 mg/kg (Albertoni 1884). In intermediate-duration oral studies, reduction in the nerve conduction velocity of rats exposed via drinking water at 650 mg/kg/day (Ladefoged et al. 1989) and excessive salivation in rats exposed by gavage at 2,500 mg/kg/day ≥27 days (American Biogenics Corp. 1986) were found. Absolute brain weight was lower in the gavaged rats at the 13-week sacrifice, but no histopathological lesions were found. No histopathological lesions were found in any of numerous central and peripheral nervous system tissues of rats given 732 mg/kg/day acetone in drinking water for 12 weeks (Spencer et al. 1978). However, no clinical or histopathological evidence was observed in rats or mice treated with higher doses for 13 weeks in the drinking water study (Dietz et al. 1991; NTP 1991), suggesting that the intermittent nature of *ad libitum* dosing via drinking water did not provide high enough doses, compared with the bolus nature of a gavage dose.

The mechanism by which acetone exerts its narcotic effects is not known, but based on the available data, it cannot be attributed to histologically observable changes in the brains of animals or to electroencephalographic changes in humans. As a solvent, however, acetone may interfere with the composition of membranes, altering their permeability to ions (Adams and Bayliss 1968). That acetone distributes to the brain was demonstrated in mice (Wigaeus et al. 1982) (see Section 2.3.2.1). The narcotic effects of acetone are generally reversible.

The narcotic effects of acetone represent a concern for public health, particularly in workers exposed occupationally, as occupational exposure in the case above exceeded the time-weighted average

standard of 750 ppm, but not the short-term exposure limit of 1,000 ppm (OSHA 1989). Narcotic effects are also of particular concern for accidental ingestion of acetone-containing household products, such as nail polish remover and liquid cement. Levels of acetone in ambient air, soil, or water, or levels present at hazardous waste sites are probably not high enough to cause narcosis or coma, but more subtle neurological and neurobehavioral effects may be of concern. Furthermore, acetone potentiates the neurotoxicity of 2,5-hexanedione by an unknown mechanism (Ladefoged et al. 1989; Lam et al. 1991; Strange et al. 1991) (see Section 2.6). Thus, coexposure to these neurotoxic ketones is of greater concern than exposure to either alone.

Reproductive Effects. No studies were located regarding reproductive effects in humans after oral or dermal exposure to acetone. Information regarding reproductive effects in humans after inhalation exposure is limited to reports of premature menstrual periods by 3 of 4 women exposed to 1,000 ppm acetone for 7.5 hours (Stewart et al. 1975), the lack of a statistically significant increased incidence of miscarriage in female laboratory workers exposed to a variety of solvents, including acetone (Axelsson et al. 1984), and an unreliable report of pregnancy complications in women factory workers exposed to acetone in Russia (Nizyaeva 1982).

Information regarding reproductive effects in animals after inhalation exposure is also limited. In an inhalation developmental study in rats and mice, no effects were found on the number of implants/litter, percent live pups/litter, or mean percent resorptions/litter (NTP 1988). No studies were located regarding reproductive effects in male animals, histological effects on reproductive organs of male or female animals, or the reproductive outcomes and other indices of reproductive toxicity in animals after inhalation exposure to acetone.

Reproductive effects (reduced reproductive index and increased duration of gestation) were found in pregnant mice exposed orally to 3,500 mg/kg/day during gestation (EHRT 1987). Intermediate-duration oral studies have shown that acetone produces reproductive effects in male Sprague-Dawley rats, but not male Wistar rats or male mice. Exposure of male Wistar rats to 1,071 mg/kg/day acetone in drinking water for 6 weeks did not affect successful mating to untreated females, number of pregnancies, number of fetuses, testicular weight, seminiferous tubule diameter, and testicular lesions (Larsen et al. 1991). However, statistically significantly increased relative testis weight (possibly due to decreased body weight), decreased sperm motility, caudal weight and epididymal weight, and increased incidences of abnormal sperm, but no histopathological testicular lesions, were found in male

Sprague-Dawley rats treated with 3,400 mg/kg/day acetone in drinking water for 13 weeks (NTP 1991). As discussed by NTP (1991), these effects on spermatogenesis are similar to those seen in alcoholics, and could be associated with the similarities in metabolism of acetone and ethanol. Vaginal cytology examinations of the female rats revealed no effects, and similar evaluation of male and female mice revealed no effects. While differences in susceptibility might account for the different results in Wistar and Sprague-Dawley rats, the Wistar rats were treated with a lower dose for a shorter duration. However, sex differences in rats, and species differences between male rats and male mice appear to exist.

No indication that dermal exposure of female mice results in histopathological effects in reproductive organs was found in an analysis of female SENCAR mice used as acetone controls in a skin painting study of formaldehyde (Ward et al. 1986).

The available data are too limited to predict whether exposure of humans to acetone under any conditions would result in reproductive effects. The finding of shortened menstrual cycles in women has not been corroborated.

Developmental Effects. No studies were located regarding developmental effects in humans after oral or dermal exposure to acetone. Information regarding developmental effects in humans after inhalation exposure is limited to a report that found no statistically significant increased incidence of miscarriage, perinatal death rate, or malformations of offspring in female laboratory workers exposed to a variety of solvents including acetone (Axelsson et al. 1984) and to an unreliable report of fetal death and low birth weight and length of neonates in female factory workers exposed to acetone in Russia (Nizyaeva 1982).

Developmental effects have been found in animals after inhalation and oral exposure. In rats exposed by inhalation to acetone during gestation, the only effect was a statistically significantly decreased mean male and female fetal body weight at 11,000 ppm, the same concentration at which dams displayed reduced body weight during gestation, reduced uterine weight, and reduced extragestational weight (NTP 1988). Mice similarly exposed were more susceptible than rats; at 6,600 ppm, statistically significantly increased incidence of late resorption, decreased fetal weight, and significantly increased incidence of reduced stemebral ossification were observed, along with increased absolute and relative liver weight of dams. Thus acetone produced fetotoxicity in rats and mice at concentrations

that were maternally toxic. Developmental toxicity was also found in mice after oral treatment of the dams with 3,500 mg/kg/day during gestation, such as reduced postnatal pup survival and reduced average weight of each live pup/litter on postpartum day 0 (EHRT 1987). Some of the dams treated at this dose displayed neurological signs of toxicity and died. Fetuses or pups were not examined for internal malformations or skeletal anomalies. No studies were located regarding developmental effects in animals after dermal exposure to acetone.

Acetone has been tested in attempts to develop *in vitro* methods for assessing developmental toxicity. Acetone at a concentration range of 0.l-1.0% (v/v) in the incubation medium had no effects on growth or malformations of 9.5 day postimplantation rat embryos or on growth and vascularization of the yolk sac (Schmid 1985). Negative results were also obtained for growth of 11 day mouse embryo limb buds at acetone concentrations of 10-100 mg/mL (Guntakatta et al. 1984). However, 10.5 day whole rat embryo cultures failed to grow and differentiate and eventually died at an acetone concentration of 2.5% (v/v) (Kitchin and Ebron 1984). A concentration of 0.5% acetone reduced yolk sac diameter and significantly increased the percentage of abnormal embryos (enlarged pericardium). At 0.1% acetone, abnormal brain development and edematous mandibular arches were also observed. Although results of studies conducted *in vitro* are difficult to extrapolate to *in vivo* exposure, acetone and its metabolites were found in fetuses from rats injected intravenously with 100 mg/kg acetone on gestational day 19, indicating transplacental transfer (Peinado et al. 1986).

Thus, acetone appears to be toxic to rat and mouse fetuses at maternally toxic inhalation concentrations and to developing neonatal mice at maternally toxic oral doses. Mice appear to be more susceptible than rats in *in vivo* studies. From limited information, acetone does not appear to be teratogenic in animals in *in vivo* experiments. Whether acetone would cause developmental toxicity in humans under any exposure conditions is not known, but concentrations and doses used in the animal studies were much higher than are likely to be experienced by humans.

Genotoxic Effects. No studies were located regarding the genotoxicity of acetone in humans or animals after inhalation, oral, or dermal exposure. The results of *in vivo* studies conducted by intraperitoneal injection are summarized in Table 2-4. Negative results were obtained in the micronucleus test in Chinese hamsters (Basler 1986) and for cell transformation in fetal cells from pregnant hamsters (Quarles et al. 1979a, 1979b). In addition, tests for gene mutation in silk worms exposed by an unspecified route were negative (Kawachi et al. 1980). Acetone has been tested for

TABLE 2-4. Genotoxicity of Acetone *In Vivo*

Species (test system)	End point	Results	Reference
Chinese hamsters	Micronuclei in erythroycytes	—	Basler 1986
Pregnant hamsters	Cell transformation in fetal cells	—	Quarles et al. 1979a, 1979b
Silk worms	Gene mutation	—	Kawachi et al. 1980

— = negative result

genotoxicity in numerous assays *in vitro*, and results of representative studies are summarized in Table 2-5. Results were negative for reverse mutation in all tested strains of *Salmonella typhimurium* (DeFlora 1981; DeFlora et al. 1984; Ishidate et al. 1984; Kawachi et al. 1980; McCann et al. 1975; Yamaguchi 1985), in the ret assay in *Bacillus subtilis* (Kawachi et al. 1980) with and without metabolic activation, and for prophage induction (De Marini et al. 1991; Rossman et al. 1991; Vasavada and Padayatty 1981) and DNA binding (Kubinski et al. 1981) in *Escherichia coli.* However, with enzyme-generated triplet acetone (Menck et al. 1986) or photo-generated triplet acetone (Rahn et al. 1974), results were positive for DNA damage in *E. coli* lambda prophage (Menck et al. 1986) and DNA chain breaks and thymidine dimers in *E. coli* (Rahn et al. 1974). Triplet acetone, which is electronically excited in one of the methyl groups, can be generated by endogenous enzymatic reactions or by photochemical reactions (Menck et al. 1986). Thus, the relevance of the DNA damage induced by triplet acetone to human exposure scenarios to acetone is questionable. Results were mixed in fungi (Abbandandolo et al. 1980; Albertini 1991; Zimmermann 1983; Zimmermann et al. 1984, 1985), and results for gene mutation were negative in *Arubidopsis thaliana* seeds (Gichner and Veleminsky 1987). Results have usually been negative in assays for cell transformation, chromosomal aberrations, sister chromatid exchange, colony formation inhibition, and gene mutation in cultured animal cells, and for sister chromatid exchange and unscheduled DNA synthesis in cultured human fibroblasts and skin epithelial cells (see Table 2-5). However, some positive results were obtained for chromosomal aberrations in Chinese hamster fibroblasts (Ishidate et al. 1984) and hamster lung fibroblasts (Kawachi et al. 1980). Acetone also inhibited metabolic cooperation (intracellular communication) in Chinese hamster V79 cells (Chen et al. 1984) and produced chromosome malsegregation in porcine brain tubulin (Albertini et al. 1988). The overwhelming evidence is that acetone is, at best, weakly genotoxic. Genotoxicity assay conditions vary widely, and probably account for different results in similar cell systems.

Because of its solvent properties and mostly lack of genotoxic effects, acetone is often used as a solvent for testing the genotoxicity of other chemicals and as the solvent control in these assays (Nestmann et al. 1985; Norppa 1981; Norppa et al. 1981). Acetone was used as the solvent control to study the promoting activity of 12-O-tetradecanoylphorbol 13-acetate in a 2-stage cell transformation assay in the BALB/3T3 cell line (Sakai and Sato 1989). No indication that acetone promoted the transforming activity of nine known genotoxic and carcinogenic chemicals was found.

TABLE 2-5. Genotoxicity of Acetone *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium	Reverse mutation			DeFlora 1981; DeFlora et al. 1984
TA98		No data	—	
TA100		No data	—	
TA1535		No data	—	
TA1537		No data	—	
TA1538		No data	—	
S. typhimurium	Reverse mutation			Yamaguchi 1985
TA100		—	—	
TA98		—	—	
S. typhimurium	Reverse mutation			Ishidate et al. 1984
TA92		—	No data	
TA94		—	No data	
TA98		—	No data	
TA100		—	No data	
TA1535		—	No data	
TA1537		—	No data	
S. typhimurium	Reverse mutation			McCann et al. 1975
TA98		—	No data	
TA100		—	No data	
TA1535		—	No data	
TA1537		—	No data	
S. typhimurium	Reverse mutation			Kawachi et al. 1980
TA100		—	—	
TA98		—	—	

TABLE 2-5. Genotoxicity of Acetone *In Vitro (continued)*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Escherichia coli ($WP2_s(\lambda)$)	Prophage λ induction	—	—	DeMarini et al. 1991; Rossman et al. 1991
E. coli (λ phage)	DNA damage	+[a]	No data	Menck et al. 1986
E. coli CR63 colitis bacteriophage	Transfection (induction of phage)	—	—	Vasavada and Padayatty 1981
E. coli B(3)T	DNA chain breaks	+[a]	No data	Rahn et al. 1974
	thymidine dimers	+[a]	No data	
E. coli	DNA binding	—	—	Kubinski et al. 1981
Bacillus subtilis	Rec assay	—	—	Kawachi et al. 1980
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae D61.M	Aneuploidy	No data	+	Zimmermann 1983; Zimmerman et al. 1984, 1985
S. cerevisiae D61.M	Mitotic chromosome malsegregation	No data	+	Albertini 1991
S. cerevisiae D61.M	Increased frequency of resistant colonies	No data	—	Albertini 1991
Saccharomyces pombe	Forward mutation	—	—	Abbandandolo et al. 1980
Plants:				
Arabidopsis thaliana seeds	Gene mutation	No data	—	Gichner and Veleminsky 1987
Mammalian cells:				
Syrian hamster embryo cells	Cell transformation	No data	—	Di Paolo et al. 1969
Syrian hamster embryo cells	Cell transformation	No data	—	Pienta 1980
Chinese hamster ovary cells	Chromosomal aberrations	—	—	Tates and Kriek 1981
Chinese hamster fibroblasts	Chromosomal aberrations	No data	+	Ishidate et al. 1984

TABLE 2-5. Genotoxicity of Acetone *In Vitro (continued)*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Hamster lung fibroblasts	Chromosomal aberrations	No data	+	Kawachi et al. 1980
Chinese hamster ovary cells	Sister chromatid exchange	—	—	Tates and Kriek 1981
Chinese hamster cells	Sister chromatid exchange	No data	—	Abe and Sasaki 1982
Hamster lung fibroblasts	Sister chromatid exchange	No data	—	Kawachi et al. 1980
Chinese hamster V79 cells	Inhibition of metabolic cooperation (intracellular communication)	No data	+	Chen et al. 1984
Chinese hamster V79 cells	Inhibition of colony formation	No data	—	Chen et al. 1984
AKR leukemia virus-infected mouse embryo cells	Cell transformation	No data	—	Rhim et al. 1974
Mouse lymphoma TK cells	Gene mutation	No data	—	Amacher et al. 1980
Rat embryo culture	Cell transformation	No data	—	Freeman et al. 1973
Rat embryo cells infected with Rauscher leukemia virus	Cell transformation; ouabain resistance	— —	— —	Mishra et al. 1978
Porcine brain tubulin	Chromosome malsegregation	No data	+	Albertini et al. 1988
Human fibroblasts	Sister chromatid exchange	No data	—	Kawachi et al. 1980
Human fibroblasts	Sister chromatid exchange	No data	—	Abe and Sasaki 1982
Human skin epithelial cells	unscheduled DNA synthesis	No data	—	Lake et al. 1978

[a]Activation to triplet state

— = negative result; + = positive result; DNA = deoxyribonucleic acid

The weight of evidence for the genotoxicity indicates that acetone poses little threat for genotoxic effects in humans exposed to acetone under any conditions.

Cancer. No studies were located regarding cancer in humans after oral or dermal exposure. A retrospective mortality study of workers exposed to time-weighted-average acetone concentrations of 380-1,070 ppm at a cellulose fiber plant where acetone was used as the only solvent found no significant excess risk of death from any cause, including malignant neoplasm, compared with rates for the U.S. general population (Ott et al. 1983a, 1983b).

No studies were located regarding cancer in animals after inhalation or oral exposure to acetone. In an analysis of the histopathology in female SENCAR mice used as acetone controls in a skin painting study of formaldehyde, no neoplastic lesions associated with acetone exposure were found (Ward et al. 1986). Furthermore, acetone was negative as a tumor promoter for formaldehyde. In addition, no evidence was found that acetone was a skin carcinogen when used as a negative control for organosilanes (DePass et al. 1989) or flame retardants (Van Duuren et al. 1978) in skin painting studies in mice. Acetone was also negative as a tumor initiator (Roe et al. 1972) and as a tumor promoter for 7,12-dimethylbenz[a]anthracene (Roe et al. 1972; Van Duuren et al. 1971; Weiss et al. 1986).

EPA has classified acetone in Group D, that is, not classifiable as to human carcinogenicity due to the lack of data concerning carcinogenicity in humans and animals (IRIS 1992). Acetone has not been classified by the National Toxicology Program (NTP) or the International Agency for Research on Cancer (IARC).

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

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

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

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

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Acetone

Acetone concentrations in expired air, blood, and urine have been monitored in a number of studies of humans exposed to acetone in the workplace as well as in controlled laboratory situations, and correlations with exposure levels have been found. However, acetone is cleared from breath, urine, and blood within 1-3 days, so these methods are useful for monitoring only for recent exposure to acetone. In addition, these methods can be used to detect or confirm relatively high exposure to

acetone, such as what might occur in the workplace or from accidental ingestion, but they cannot be used to detect exposure in the general population at levels reasonably likely to occur outside the workplace. The detection of acetone odor in the breath can alert a physician that a nondiabetic patient has been exposed to acetone (Harris and Jackson 1952; Strong 1944). It should be noted that exposure to other chemicals that are metabolized to acetone, such as isopropyl alcohol, could also lead to elevated blood, expired air, or urinary levels of acetone. Levels of endogenous acetone can fluctuate greatly due to normal diurnal variations (Wildenhoff 1972). In addition, physical exercise (Koeslag et al. 1980); nutritional status and fasting (Jones 1987; Kundu et al. 1993; Levy et al. 1973; Lewis et al. 1977; Neiman et al. 1987; Reichard et al. 1979; Rooth and Carlstrom 1970; Williamson and Whitelaw 1978); trauma (Smith et al. 1975); and pregnancy and lactation (Bruss 1989; Paterson et al. 1967) place high energy demands upon the body, resulting in increased fatty acid utilization and higher than average blood levels of acetone. Diabetes (Kobayashi et al. 1983; Levey et al. 1964; Reichard et al. 1986; Rooth 1967; Rooth and Ostenson 1966) and alcohol use (Phillips et al. 1989; Tsukamoto et al. 1991) may result in high levels of endogenous acetone. Infants and young children typically have higher acetone in their blood than adults due to their higher energy expenditure (Peden 1964). These factors and physiological states can complicate measuring acetone levels in blood, breath, and urine for biomonitoring purposes.

In a group of 115 workers, alveolar air samples obtained during the workshift were collected at the same time as breathing zone acetone concentrations (Brugnone et al. 1980). The mean ratio of alveolar air acetone and breathing zone acetone was 0.288. Correlations were high between alveolar air concentrations and breathing zone concentrations. Because the alveolar air samples and breathing zone concentrations were collected at the same time, and since the equilibration of alveolar air with environmental air requires some time, the alveolar samples might not necessarily reflect the environmental concentration. Similar results were obtained in a group of 20 workers in a shoe factory in which the mean environmental air concentrations ranged from 10 to 12 ppm at four sampling times (Brugnone et al. 1978). The mean alveolar concentrations ranged from 2.75 to 3.75 ppm at three sampling times during the workshift. The correlation was good between workroom air concentration and alveolar air concentration, indicating that alveolar air concentrations of acetone are useful for monitoring concurrent occupational exposure to acetone. In a group of 110 male workers exposed to acetone for an average of 14.9 years, alveolar air samples were collected before work and at the end of work on 2 consecutive days (Fujino et al. 1992). The breathing zone concentrations of acetone were measured for each individual with personal monitors and ranged from 0 to about 1,200 ppm, with

most concentrations between 100 and 500 ppm. The average concentration of acetone in alveolar air before exposure on the first day was 2.95 ppm. Alveolar air concentrations at the end of the workday (range of about 20 to 300 ppm, average not reported) correlated strongly with exposure concentrations (r=0.65). It was estimated that the alveolar air concentrations corresponding to the ACGIH threshold limit value (TLV) of 750 ppm and to the Japan Association of Industrial Health acceptable concentration of 200 ppm were 177 and 56.2 ppm, respectively.

Expired air concentrations of acetone have also been studied in volunteers exposed to acetone in controlled laboratory situations. In 11 men and 11 women exposed to 237 ppm acetone for 2 or 4 hours, alveolar breath samples collected immediately after exposure contained mean levels of acetone of 21.5 ppm in those exposed for 2 hours and 25.8 ppm in those exposed for 4 hours (Dick et al. 1989). The alveolar air concentrations of acetone dropped to 12.8 ppm by 90 minutes after the 4-hour exposure and to background levels of 0.6 ppm by 20 hours postexposure. In humans exposed to acetone at ≤1,250 ppm for ≤7.5 hours/day in a complex protocol for ≤6 weeks, the rate of respiratory excretion was a function of the duration, and the concentration of acetone in breath after exposure was directly related to the time-average concentration during exposure, with constant duration (Stewart et al. 1975). The length of time after exposure in which acetone could be detected in breath was related to the magnitude of exposure; acetone was still readily detectable 16 hours after exposure to 1,000 or 1,250 ppm for 7.5 hours. Therefore, breath analysis can be used as a rapid method to estimate the magnitude of recent acetone exposure, but has limited usefulness for more remote exposure because elimination in expired air is generally complete within 1 day.

As discussed in Section 2.3.4.1, the level and nature of physical activity, the exposure concentration, the duration of exposure, and gender can influence the rate and amount of acetone elimination in the breath (DiVincenzo et al. 1973; Nomiyama and Nomiyama 1974a, 1974b; Pezzagno et al. 1986; Wigaeus et al. 1981). In general more acetone is expired faster following exposure to high concentrations than to low concentrations (DiVincenzo et al. 1973). Doubling the duration of exposure almost doubles the total amount of acetone expired. Exercise during exposure eliminates nearly twice the amount in expired air compared with exposure to the same concentration at rest, due to increased uptake from increased pulmonary ventilation. Furthermore, exercising at stepwise increments in workload during exposure results in greater respiratory elimination than exercising at a constant workload (Wigaeus et al. 1981). Women appeared to expire acetone more slowly than men,

but the total expired by women was not statistically significantly different than the total expired by men (Nomiyama and Nomiyama 1974a, 1974b).

Acetone is mainly excreted in the expired air after oral exposure as well as after inhalation exposure (see Section 2.3.4.2). Since urinary clearance of acetone is minimal, the calculated clearance of acetone from the lungs was 29 ml/minute or 0.39 ml/minute/kg for a patient who ingested nail polish remover using an average minute ventilation of 9.65 L/minute based on the patient's age, weight, and sex (Ramu et al. 1978). With a volume of distribution of 0.82 L/kg, the calculated half-life was 25 hours.

Monitoring of expired air for acetone exposure should take into consideration background levels of acetone, since acetone is produced endogenously in the body, especially during fasting and in diabetics. In addition, the ingestion of ethanol can influence the breath levels of acetone. Endogenous levels of acetone in normal humans averaged 0.56 ppm (Phillips and Greenberg 1987). Endogenous levels of acetone in alveolar air in a group of volunteers in an experimental study averaged 0.108 ppm (Wigaeus et al. 1981). In healthy men who had fasted for 12 hours, the breath acetone levels ranged from 0.96 to 1.7 ppm (Jones 1987). Fasting for 36 hours resulted in average acetone breath levels of 14-66 ppm. However, in fasting men who ingested 0.25 g/kg of ethanol, the breath acetone levels decreased by 40% after a 12-hour fast and by 18% after a 36-hour fast (Jones 1988).

Acetone is metabolized to carbon dioxide (see Section 2.3.3), which is eliminated in expired air (see Section 2.3.4). However, since carbon dioxide is the main constituent of normal respired air, expired carbon dioxide has not been monitored to determine acetone exposure.

Although unchanged acetone is excreted mainly by the lungs, urinary levels are sufficiently high for monitoring purposes. In a group of 104 workers employed at factories in which breathing zone levels of acetone ranged from <242 to <1,452 ppm, urine was collected before the workshift and 4 hours later (Pezzagno et al. 1986). A close correlation was found between the time-weighted average workroom concentration and the urinary concentration of acetone. The equation obtained was: urinary concentration (μmol/L) = 0.033 x time-weighted average environmental concentration (umol/m^3) = 0.005 (r=0.94, n=104). In another study of 28 workers, personal breathing zone monitoring revealed wide variation depending on the type of job and ranged from <1 to 30 ppm (Kawai et al. 1990a). Results of stationary monitoring revealed workroom concentrations ranging from

1.4 to 16.2 ppm. Urine was collected at the end of the workshift, and acetone was detected in the urine of all the workers. The concentration of acetone in urine was linearly correlated with the breathing zone concentration as follows: acetone in urine (mg/L) = 0.10 + 0.40 x breathing zone concentration (ppm) (r=0.90, p<O.01). Therefore, urinary levels of acetone are useful for monitoring occupational exposure. In another study, postshift urinary levels of acetone in 45 workers exposed to 0-70 ppm acetone ranged from 0 to 17.5 mg/L (Kawai et al. 1992). The background urinary level of acetone in nonexposed subjects was 1.5 mg/L. Acetone levels in preshift urine samples were significantly higher than background levels when acetone exposure on the previous day was >15 ppm, but there was no significant difference between background urine levels and preshift urine levels when acetone exposure on the previous day was ≤15 ppm. In a group of 110 males workers exposed to acetone for an average of 14.9 years, urine samples were collected before work and at the end of work for 2 consecutive days (Fujino et al. 1992). The breathing zone concentrations of acetone were measured for each individual with personal monitors and ranged from 0 to about 1,200 ppm, with most concentrations between 100 and 500 ppm. The average urinary concentration before exposure on the first day was 2.44 mg/L. Urinary levels at the end of the workshift (range of about 5 to 150 ppm, average not reported) correlated strongly with exposure concentration (r=0.71). It was estimated that the urinary concentrations corresponding to the ACGIH TLV of 750 ppm and to the Japan Association of Industrial Health acceptable concentration of 200 ppm were 76.6 and 21.6 mg/L, respectively.

Acetone has also been detected in the urine of 15 subjects exposed to acetone under controlled laboratory conditions. In volunteers exposed to 23-208 ppm for 2-4 hours, the urinary concentrations of acetone immediately after exposure ranged from 18.8 to 155.2 μmol/L and displayed statistically significant linear relationships with the exposure concentrations (Pezzagno et al. 1986). The regression equation for subjects exposed for 2 hours at rest was: acetone in urine (μmol/L) = 0.0125 x environmental concentration (μmol/m^3) + 5.87 (r=0.98, n=5). For subjects exposed for 4 hours at rest the equation was: acetone in urine (μmol/L) = environmental concentration (μmol/m^3) + 6.97 (r=0.96, n=5). For the subjects exposed for 2 hours with exercise, the equation was: acetone in urine (pmol/L) = environmental concentration (μmol/m^3) - 4.52 (r=0.99, n=5). At 4 hours after exposure, the urine concentration increased to 120% of that measured immediately after exposure, then fell to 65% at 7 hours, 45% at 9 hours, 35% at 12 hours, and 15% at 20 hours. Urinary acetone was completely cleared within 20 hours from subjects exposed to 242 or 542 ppm for 2 hours, regardless of whether or not they had exercised during exposure (Wigaeus et al. 1981). In a group of subjects exposed to acetone vapors for about 6 hours, urinary levels of acetone peaked within the first hour after exposure

to 1.8 mg/dL at 250 ppm, 2.9 mg/dL at 500 ppm, and 5.3 mg/dL at 1,000 ppm and declined rapidly after exposure to control levels within 24, 32, and 48 hours, respectively (Matsushita et al. 1969b). In subjects exposed to 250 ppm for 6 hours/day for 6 days either at rest or during exercise, the urinary levels declined to normal by the next morning each day and within 48 hours after the last exposure day, regardless of whether or not they had exercised (Matsushita et al. 1969a). However, in subjects exposed to 500 ppm 6 hours/day for 6 days, the level of acetone in the urine fell each day, but not to background levels. After the last day of exposure, urinary levels declined to background levels within 3 days. Background urinary levels of acetone in these subjects were about 0.1 mg/dL. Therefore, the rate of urinary clearance is dependent on the magnitude of exposure.

Acetone can also be detected in urine after oral exposure. In a patient who was admitted to the hospital in a comatose condition after ingesting sake and liquid cement containing 18% acetone (231 mg/kg), urinary clearance of acetone was followed, but after he had been subjected to gastric lavage (Sakata et al. 1989). Urine levels of acetone decreased gradually from 123 μg/mL at 5 hours after ingestion to about 61 μg/mL at 19 hours. Acetone then disappeared more rapidly from the urine.

Formic acid was detected in the urine of rats collected for 7 days after exposure to 62,000 ppm acetone in air, and was excreted at a rate of 344 μg formic acid/hour, compared with controls that excreted formic acid at a rate of 144 μg/hour (Hallier et al. 1981). The authors concluded that the low rate of formic acid excretion by rats suggests that 24 hours is an insufficient period of time for following formic acid excretion in order to biomonitor acetone exposure in humans.

Blood levels of acetone can also be useful for exposure monitoring, but blood sampling is less desirable because it is invasive. In a group of 110 males workers exposed to acetone for an average of 14.9 years, blood samples were collected before work on the first day and at the end of work on the second day (Fujino et al. 1992). The breathing zone concentrations of acetone were measured for each individual with personal monitors and ranged from 0 to about 1,200 ppm, with most concentrations between 100 and 500 ppm. The average blood concentration before exposure on the first day was 3.80 mg/L. Blood levels at the end of the workshift (range of about 2 to 225 mg/L, average not reported) correlated strongly with exposure concentration ($r=0.65$). It was estimated that the blood concentrations corresponding to the ACGIH TLV of 750 ppm and to the Japan Association of Industrial Health acceptable concentration of 200 ppm were 118 and 41.4 mg/L, respectively. Subjects exposed to 100 or 500 ppm for 2 or 4 hours had a blood acetone clearance half-life of 3 hours

(DiVincenzo et al. 1973). The rate of blood elimination was constant regardless of blood acetone concentration. In volunteers exposed to 237 ppm acetone, blood levels of acetone averaged 2.0 μg/mL preexposure, 9.0 μg/mL after 2 hours of exposure, 15.3 μg/mL after 4 hours of exposure, 11.9 μg/mL at 90 minutes postexposure, and 1.5 μg/mL at 20 hours postexposure (Dick et al. 1989). Therefore, elimination of acetone from blood was complete 20 hours after exposure. Results were similar for subjects exposed to acetone vapors for =6 hours (Matsushita et al. 1969b). Maximum blood levels of acetone achieved and blood clearance of acetone were exposure concentration-related, but not in direct proportion. At an exposure level of 250 ppm, the maximum blood level was 2 mg/dL and declined to background level within 24 hours. At an exposure level of 500 ppm, the maximum blood level was 4.7 mg/dL and declined to background level within 32 hours. At an exposure level of 1,000 ppm, the maximum blood level of 6.0 mg/dL declined to background level within 48 hours. In subjects exposed 6 hours/day for 6 days, maximum blood levels on each day were similar to those seen in the subject exposed only 1 day (Matsushita et al. 1969a). Blood levels declined to background levels on the morning after exposure on each day when the exposure concentration was 250 ppm. With an exposure concentration of 500 ppm, however, the blood levels declined each day, but not to background levels. As with urinary clearance, blood clearance of acetone at the end of the 6-day exposure period declined to background within 2 days at 250 ppm and within 3 days at 500 ppm. Background blood levels of acetone in these subjects were about 0.1 mg/dL. In subjects exposed to 242 or 542 ppm for 2 hours, the arterial blood concentration 1 hour after exposure plotted as a function of total uptake gave a linear relationship, indicating that an arterialized capillary sample during or after exposure may be useful for exposure monitoring (Wigaeus et al. 1981). In humans exposed to acetone ≤1,250 ppm for ≤7.5 hours/day in a complex protocol for ≤6 weeks, the concentration of acetone in venous blood was directly related to the vapor concentration and duration of exposure and inversely related to the time elapsed following exposure (Stewart et al. 1975). Using a physiologically-based pharmacological model, Leung and Paustenbach (1988) calculated a biological exposure index of 35 mg acetone/L blood for occupational exposure. The authors reported a background acetone blood level of 2 mg/L. This value is in agreement with normal background levels determined in other studies: 0.016 mM (0.93 mgn) (Gavin0 et al. 1986); 0.03 mmol/L (1.74 mg/L) (Trotter et al. 1971); 2100 ppb (2.1 mg/L) (Ashley et al. 1992).

Similar rates of blood acetone clearance occur after oral exposure. In a patient admitted to the hospital in a comatose condition after ingesting liquid cement containing 18% acetone (231 mg/kg), the plasma level of acetone was 110 μg/rnL at 5 hours after ingestion and declined to 65 μg/rnL at

18 hours, to 60 μg/mL at 20 hours, and to <5 μg/mL at 48 hours (Sakata et al. 1989). The gastric contents of a patient were analyzed using infrared spectrophotometry and found to contain 1 mL acetone/100 mL (Fastlich 1976). This analytical method was developed to detect volatile solvents in gastric contents due to accidental ingestion of these solvents.

Acetone has been identified in breast milk of lactating women (Pellizzari et al. 1982). According to the authors, mother's milk is an attractive medium for biomonitoring purposes because sample collection is reasonably straight-forward, milk contains a high amount of fat, so that fat-soluble pollutants may be found at higher concentrations in milk than in blood or urine, large volumes are easily collected, and the population of nursing mothers is relatively large. A disadvantage is the fact that only young to middle-age females are nursing, making extrapolation to the general population difficult.

As discussed in Section 2.9.3, an abstract indicated that acetone increased the levels of DNA adducts in rats exposed via drinking water (Cunningham and Gold 1992).

2.5.2 Biomarkers Used to Characterize Effects Caused by Acetone

The most consistently observed effect of acetone exposure in animals is the induction of microsomal enzymes, particularly of cytochrome P-450IIEl (see Sections 2.2.2.2, 2.35, and 2.6). The enzyme induction has been associated with increased liver weights and hepatocellular hypertrophy due to the increased protein content (NTP 1991). Acetone itself is only moderately toxic to the liver of animals, as most studies have found no clinical or histological evidence of liver damage. However, increased levels of serum alanine aminotransferase, which constitutes clinical evidence of liver damage, have been found in rats in one study (American Biogenics Corp. 1986). Cytochrome P-450IIEl is associated with the metabolism of acetone itself, but acetone is not metabolized to toxic intermediates (see Section 2.3). However, the induction of this enzyme by acetone is the mechanism by which acetone potentiates the hepatotoxicity, nephrotoxicity, genotoxicity, and perhaps the reproductive and hematological toxicity of other chemicals (see Section 2.6). Cytochrome P-450IIEl can be induced by a variety of other factors, such as exposure to ethanol, fasting, and experimental diabetes (Johansson et al. 1986; Puccini et al. 1990); therefore, the induction is not specific to acetone. Moreover, the detection of enzyme induction might require invasive methods, such as liver biopsy. As discussed in Section 2.9.3, an *in vivo* probe is being developed to identify human populations with elevated levels

of cytochrome P-45011El. These persons are thought to be at greater risk for developing the carcinogenicities and cytotoxicities related to P-45011El activity.

Exposure of animals to acetone has resulted in degeneration of apical microvilli in renal tubules (Brown and Hewitt 1984) and enhancement of nephropathy commonly seen in aging rats (NTP 1991), but these effects have not been associated with increased levels of blood urea nitrogen.

As is typical of many organic solvents, acetone is irritating to respiratory mucosa, the skin, and eyes. Acetone exposure can also result in such nonspecific narcotic effects as headache, dizziness, lightheadedness, confusion, unconsciousness (DiVincenzo et al. 1973; Matsushita et al. 1969a, 1969b; Nelson et al. 1943, Raleigh and McGee 1972; Ross 1973), some neurobehavioral and hematological effects (Dick et al. 1989; Matsushita et al. 1969a; Stewart et al. 1975), and perhaps menstrual disorders (Stewart et al. 1975). In addition, patients who had hip casts applied with acetone as the setting fluid became nauseous, vomited blood, and had a strong odor of acetone in the breath. These symptoms were associated with the subsequent development of unconsciousness (Harris and Jackson 1952; Strong 1944). The detection of a strong acetone odor on the breath and nausea could alert physicians to the development of more serious sequelae, such as gastrointestinal hemorrhage and narcosis.

Since acetone is a ketone, acetone exposure can lead to ketosis and other diabetes-like symptoms in humans (Gitelson et al. 1966) and to reduced insulin-stimulated glucose oxidation in animals (Skutches et al. 1990). Again the detection of a strong odor of acetone on the breath, or high levels of acetone in blood or urine can alert physicians to these effects.

In male rats, acetone exposure resulted in anemia as detected by hematological parameters (American Biogenics Corp. 1986; NTP 1991), and in increased testis weight, decreased sperm motility, caudal and epididymal weight, and increased incidences of abnormal sperm (NTP 1991). Hematological tests and tests for sperm motility and abnormalities could be used to screen humans for possible hematological and fertility effects.

Dermal exposure of humans to acetone irritated the skin, which when examined by light and electron microscopy, showed signs of degenerative changes in the epidermis (Lupulescu and Birmingham 1976; Lupulescu et al. 1972, 1973). Decreased protein synthesis was also found (Lupulescu and Birmingham

1975). Overt signs of skin irritation could alert physicians to possible degenerative changes. Allergic reactions to acetone can be detected by patch testing (Tosti et al. 1988).

As most of the effects of acetone are not specific to acetone, there is no reliable biomarker of effect that can be used to detect or screen for possible effects from exposure to acetone at levels reasonably likely to occur outside the workplace or from accidental ingestion.

For more detailed discussion of the effects caused by acetone see Section 2.2. Further information on biomarkers for specific organ systems (immune, renal, hepatic) can be found in ATSDR/CDC (1990) and on neurological effects in OTA (1990).

2.6 INTERACTIONS WITH OTHER SUBSTANCES

While acetone by itself is only moderately toxic, it potentiates the toxicity of a variety of chemicals, including halogenated alkanes and alkenes, benzene, dichlorobenzene, ethanol, 2,5-hexanedione, nitrosamines, acetonitrile, and acetaminophen. By far, the most extensively studied interactions are those with carbon tetrachloride and chloroform. In most of the interactions discussed below, acetone exerts its potentiating effect by inducing microsomal mixed function oxidases, in particular cytochrome P-45OIIEl and P-450IIEl-dependent enzyme activities, that bioactivate the other chemicals to reactive metabolites.

Halogenated Alkanes and Alkenes. No studies were located regarding the effects of coexposure of humans to acetone and carbon tetrachloride. However, acetone, a metabolite of isopropyl alcohol, was implicated in a study of workers in a isopropyl alcohol packaging plant who became ill after accidental exposure to carbon tetrachloride (Folland et al. 1976). Fourteen workers became ill (nausea, vomiting, headache, and weakness or abdominal pain, dizziness, diarrhea, and blurred vision). Workers in closer proximity to isopropyl alcohol were especially affected. Renal failure and hepatitis developed in 4 of the workers with closer proximity to isopropyl alcohol. Expired air samples taken subsequently from workers during isopropyl alcohol bottling revealed strikingly elevated levels of acetone (mean = 19 ppm in workers on the bottling line and 7.5 ppm in more remote workers). The blood acetone levels were 3-30 times higher than the normal range. Thus it appeared that isopropyl alcohol, by way of acetone, predisposed the workers to the hepatotoxicity and renal toxicity induced by carbon tetrachloride.

The potentiation of carbon tetrachloride-induced hepatotoxicity and renal toxicity by acetone has been well documented in rats. Pretreatment of rats by gavage with acetone enhanced the hepatotoxicity of carbon tetrachloride, as evidenced by the statistically significantly increased relative liver weights, increased severity of histopathological lesions (necrosis, hepatocellular swelling, lipid droplets), activities of serum alanine aminotransferase and ornithine carbamoyltransferase, the serum concentration of bilirubin, and/or the liver concentration of triglycerides compared with the liver toxicity induced by carbon tetrachloride alone in several studies (Charbonneau et al. 1985; 1986a, 1986c; 1988; 1991; Plaa et al. 1973, 1982; Plaa and Traiger 1972; Traiger and Plaa 1973, 1974). Acetone treatment alone had no effect on these parameters. The potentiation increased in a doserelated manner at single doses of acetone ≥0.25 mL/kg (≥196 mg/kg); doses of ≤0.10 mL/kg (≤78 mg/kg) are ineffective (Charbonneau et al. 1986a; Plaa et al. 1982; Traiger and Plaa 1973). In rats given the minimal effective dose of acetone (196 mg/kg) twice daily for 3 days (total dose 1,177 mg/kg), carbon tetrachloride-induced liver toxicity was further enhanced over that of a single dose of 196 mg/kg acetone (Plaa et al. 1982). However, the repetitive dose of acetone (6x196 mg/kg = 1,177 mg/kg) potentiated the liver toxicity of carbon tetrachloride to a lesser extent than a single dose of 1,177 mg/kg. Administration of the noneffective dose (78 mg/kg) twice a day for 3 days (total dose 468 mg/kg) did not affect the liver toxicity of carbon tetrachloride, even though the cumulative dose of 468 mg/kg, if given as a single dose, would have been high enough to cause significant potentiation. When a dose of acetone of 1.5 mL/kg (1,177 mg/kg) was given once, divided into 6 doses of 0.25 mL/kg (196 mg/kg) over 3 days (cumulative dose 1,177 mg/kg) or into 12 doses of 0.125 mL/kg (98 mg/kg) over 3 days (cumulative dose 1,177 mg/kg), or infused intravenously over 3 days, before challenge with carbon tetrachloride, the most severe potentiation occurred with the single dose, followed by 6 divided doses, and, then by 12 divided doses. The intravenous infusion did not enhance the toxicity of carbon tetrachloride. The maximum blood levels calculated from pharmacokinetic parameters for the different acetone treatment regimens showed a direct relationship with the degree of potentiation. The results indicate that threshold blood, and hence liver, concentrations must be exceeded before potentiation occurs. Acetone pretreatment also prolonged the liver toxicity induced by carbon tetrachloride and decreased the recovery time (Charbonneau et al. 1985). With carbon tetrachloride alone, the severity of liver toxicity increased temporally in rats sacrificed 24 and 48 hours after dosing, but liver toxicity was no longer observed at 96 hours. Following pretreatment with acetone, the liver toxicity induced by carbon tetrachloride was enhanced and increased in severity at all sacrifice times, even at 96 hours. Gavage pretreatment of rats with 1,452 mg/kg/day acetone in corn oil twice weekly for ≤12 weeks, followed by carbon tetrachloride

challenge, resulted in decreased body weight gain and 35% mortality, compared with no effect on body weight gain and 5% mortality in rats given corn oil and challenged with carbon tetrachloride (Charbonneau et al. 1986c). The acetone plus carbon tetrachloride treated rats also had statistically significantly decreased relative liver weights and statistically significantly increased kidney weights at all four sacrifice times, compared with corn oil plus carbon tetrachloride rats. Bilirubin concentrations and collagen content were also enhanced. Histological examination revealed fully developed cirrhosis in the acetone plus carbon tetrachloride rats, compared with less severe cirrhosis in the corn oil plus carbon tetrachloride rats. Renal toxicity was also enhanced, as evidenced by statistically significantly elevated blood urea nitrogen levels in the acetone pretreated rats, compared with corn oil pretreated rats. It should be noted that acetone displays a greater degree of potentiation when it is administered in corn oil than in water (Charbonneau et al. 1986a, 1991), and it appears that corn oil alone can be toxic to the liver (Charbonneau et al. 1991).

Inhalation exposure of rats to acetone vapors also displays a threshold effect (Charbonneau et al. 1986a). In rats exposed to 1,000, 2,500, 5,000, 10,000, or 15,000 ppm acetone for four hours, and challenged 18 hours later with carbon tetrachloride, the liver toxicity of carbon tetrachloride was enhanced in a concentration-related manner at $\geq$2,500 ppm acetone. The noneffective concentration was 1,000 ppm. No cumulative effect of repetitive inhalation exposure to acetone on the carbon tetrachloride-induced liver toxicity was found, but maximum blood levels of acetone correlated with the degree of potentiation.

When rats were challenged with a mixture of trichloroethylene and carbon tetrachloride, the minimal effective dose of acetone required to enhance the liver toxicity of carbon tetrachloride decreased at least five-fold, indicating that mixtures of haloalkanes can cause severe liver injury, and prior exposure to acetone can markedly affect the response produced by the mixtures (Charbonneau et al. 1988).

The mechanism of acetone potentiation of carbon tetrachloride-induced liver toxicity involves the induction of mixed function oxidase microsomal enzymes. In microsomes prepared from rats treated by gavage with acetone at 2.5 mL/kg (1,961 mg/kg) and incubated with ^{14}C-carbon tetrachloride, covalent binding of radioactivity to microsomal protein increased 3-4 times that of control microsomes (Sipes et al. 1973). The time course followed the increased activity of N-nitrosodimethylamine N-demethylase, indicating enzyme induction. Furthermore, aminothiazole, an inhibitor of cytochrome P-450 and mixed function oxidase induction, reduced the potentiation by acetone of carbon

tetrachloride-induced liver toxicity (Traiger and Plaa 1973). More recent studies have indicated that the effects of acetone on the toxicity of carbon tetrachloride are caused by induction of cytochrome P-450 forms belonging to at least two gene subfamilies, i.e., P-45011B and P-45011E (Johansson et al. 1988; Kobusch et al. 1989). Complementary DNA and protein sequencing analyses have shown that these P-450 gene subfamilies are similar in rats and humans (Song et al. 1986). Acetone treatment caused a nine-fold increase in cytochrome P-450IIEl accompanied by a similar increase in the rate of nicotinamide adenine dinucleotide phosphate (NADPH)-dependent metabolism of carbon tetrachloride (Johansson et al. 1988). Acetone treatment also increased the amount of messenger ribonucleic acid (mRNA) and apoprotein of P-450IIBl l0- to 30-fold, suggesting regulation of cytochrome P-450IIBl at the transcriptional level. mRNA coding for P-45OIIEl was increased by a combination of fasting and acetone treatment, but not by treatment with acetone alone. The results suggested an enhanced rate of P-45OIIEl gene transcription, P-450IIEl mRNA stabilization, or other posttranscriptional mechanisms. The exact mechanism by which acetone increases the P-450 subfamilies is a subject of recent and on-going investigations. The findings that pretreatment of rats or rabbits with acetone results in increases in cytochrome P-45OIIEl and associated enzyme activities, but has no effect on the level of P-450IIEl mRNA suggests that regulation of acetone-induced P-450IIEl occurs at the posttranscriptional level (Hong et al. 1987; Johansson et al. 1988; Porter et al. 1989; Ronis and Ingelman-Sundberg 1989; Ronis et al. 1991; Song et al. 1986; Song et al. 1989). In microsomal and ribosomal preparations from rats administered acetone intraperitoneally, the polyribosomal distribution of cytochrome P-45OIIEl mRNA shifted, compared with controls, suggesting that the induction of P-45OIIEl by acetone involved enhanced translation efficiency through increased loading of ribosomes of P-45OIIEl mRNA (Kim et al. 1990). However, in another study, incorporation of ^{3}H-leucine into P-45OIIEl in microsomes from rats treated with acetone was lower than that in control microsomes, but the rate of translation of the P-450IIEl mRNA was about the same in both sets of microsomes, indicating that P-45OIIEl is not induced by an increase in the rate of translation of its mRNA (Song et al. 1989). Furthermore, incorporation of $NaH^{14}C0^{3}$ was three-fold less in acetone induced P-450IIEl protein than in controls. The rate of disappearance of radiolabel from P-45OIIEl in controls was biphasic, with half-lives of 7 and 37 hours for the fast and slow phase, respectively. However, in acetone-treated rats, the fast phase was absent, with a monophasic half-life of 37 hours. These results demonstrated that the induction of P-450IIEl by acetone is due primarily to protein stabilization. In microsomes and lysosomes from rats treated with acetone, cytochromes P-45OIIEl and P-450IIBl increased, but the increase was greater in microsomes (Ronis and Ingelman-Sundberg 1989; Ronis et al. 1991). Quantification of the proteins in lysosomes indicated that P-450IIEl and P-450IIBl are

degraded via an autophagosomal/autolysosomal pathway. The authors speculated that P-450IIEl is catalytically inactivated in microsomes prior to degradation in lysosomes and that acetone may interfere with the inactivation. Thus, the induction P-450IIBl appears to occur at the transcriptional level, while the induction of P-450IIEl by acetone appears to occur through stabilization of the apoprotein.

In contrast, pretreatment of mice with carbon tetrachloride enhanced the toxicity of acetone. In mice intraperitoneally pretreated with olive oil, the oral LD_{50} of acetone was 5,250 mg/kg, while in mice pretreated with a 20% solution of carbon tetrachloride in olive oil reduced the LD_{50} of acetone to 4,260 mg/kg (Tanii et al. 1986). The dose of carbon tetrachloride alone did not result in any death. The authors suggested that carbon tetrachloride inactivated the microsomal monooxygenase system, thereby inhibiting the inactivation of acetone.

Acetone also potentiates the hepato- and nephrotoxicity of chloroform. Pretreating rats with 15 mmol/kg (871 mg/kg) acetone in corn oil by gavage 18 hours prior to a challenge dose of 0.5 mL/kg chloroform in corn oil statistically significantly increased the relative kidney weight, inhibited lactate stimulated accumulation of p-aminohippurate and the accumulation of tetraethylammonium ion in kidney slices, and resulted in vacuolar degeneration in the tubular epithelium, but not necrosis, compared with corn oil controls (Hewitt et al. 1980). No effects on these parameters were observed with acetone alone or in rats pretreated with corn oil and challenged with chloroform. Acetone pretreatment also statistically significantly increased the plasma activities of alanine aminotransferase (32-fold) and ornithine carbamoyltransferase (134-fold), compared with corn oil pretreated controls challenged with chloroform, and caused balloon cells with pyknotic nuclei in the centrilobular region of the liver. Acetone alone and chloroform alone did not cause liver lesions. In rats treated by gavage with acetone in corn oil at 58, 290, 436, 581, 726, or 871 mg/kg and challenged with 0.5 mL/kg chloroform in corn oil, acetone showed a dose-dependent decrease in p-aminohippurate uptake and an increase in plasma creatinine levels, with maximum effects seen at doses between 290 and 581 mg/kg acetone (Brown and Hewitt 1984). Renal necrosis, hyaline bodies, and/or tubular casts were seen in 3/6 rats at 58 mg/kg acetone and in 4/6-5/6 rats at higher doses. Acetone pretreatment also statistically significantly increased plasma activities of alanine aminotransferase at $\geq$290 mg/kg. Balloon cells and necrosis were observed in 216 rats pretreated with 58 mg/kg and in most of the rats pretreated with $\geq$290 mg/kg. The effects of acetone pretreatment and chloroform challenge were greater than the effects of corn oil pretreatment and chloroform challenge. Pretreating rats by gavage with 0.5 mL/kg

acetone (871 mg/kg) in corn oil prior to a challenge dose of chloroform (0.5 mL/kg) in corn oil statistically significantly increased the plasma activities of alanine aminotransferase and ornithine carbamoyltransferase above that seen in rats pretreated with corn oil and challenged with chloroform, and the potentiation was maximal at 18 hours (Hewitt et al. 1987). Microsomes from the acetone treated rats showed increased activities of ethoxycoumarin O-deethylase and NADPH-dependent cytochrome c reductase and statistically significantly increased rates of covalent binding of radioactivity from ^{14}C-chloroform in the reaction medium, compared with control microsomes. Results were similar with microsomes prepared from rats treated by gavage with 2.5 mL/kg (1,961 mg/kg) acetone in corn oil. Acetone enhanced the covalent binding of radioactivity of ^{14}C-chloroform two-fold compared with control microsomes and increased the activity of N-nitrosodimethylamine N-demethylase (Sipes et al. 1973), an activity associated with cytochrome P-450IIEl. Thus, acetone increased the biotransformation of chloroform.

The involvement of cytochrome P-450IIEl was confirmed with microsomes from rats given a gavage dose of acetone (871 mg/kg) in corn oil (Brady et al. 1989). Acetone statistically significantly increased the cytochrome P-450 content, the activity of N-nitrosodimethylamine N-demethylase, and the content of cytochrome P-450IIE1, but not P-450IIB1, compared with control microsomes. Furthermore, no effect was seen on the activity of benzphetamine demethylase, an activity associated with P-45011B 1. The acetone-induced microsomes also showed a three-fold enhancement of P-450IIEl-dependent chloroform metabolism, but the activity required the presence of cytochrome b_5 No increased P-45011B l-dependent metabolism was seen. The involvement of P-450IIEl was further demonstrated by inhibition of the reaction with a monoclonal antibody to P-450IIEl and by alternate substrates for P-450IIE1, such as, pyrazole, benzene, nitrosodimethylamine, and diallyl sulfate.

Acetone also potentiates the toxicity of other halogenated alkanes. In rats injected intraperitoneally with acetone in saline at doses of 581, 1,162, 1,742, or 2,323 mg/kg 48 hours prior to a gavage dose of dichloromethane (0.4 mL/kg), statistically significantly increased blood levels of carboxyhemoglobin were observed at 21,742 mg/kg acetone, compared with controls challenged with dichloromethane (Pankow and Hoffmann 1989). The results indicated that acetone increased the metabolism of dichloromethane to carbon monoxide. Results obtained with fasting rats or rats pretreated with isoniazid, which also induces cytochrome P-450IIE1, produced similar potentiation of dichloromethane-induced carboxyhemoglobinemia, thus implicating induction of cytochrome P-450IIEl as the mechanism whereby acetone increased the metabolism of dichloromethane to carbon monoxide.

While neither bromodichloromethane or dibromochloromethane were hepatotoxic (assessed by relative liver weight and plasma activities of alanine aminotransferase and ornithine carbamoyltransferase) in rats at the sublethal doses used, acetone pretreatment at 871 mg/kg by gavage in water resulted in liver toxicity at lower challenge doses of these compounds compared to the doses that produced toxicity when these compounds were administered without acetone pretreatment (Hewitt et al. 1983). Neither bromodichloromethane or dibromochloromethane alone displayed appreciable toxicity to the kidney (assessed by relative kidney weight, accumulation of p-aminohippurate and tetraethylammonium ion in kidney slices, and blood urea nitrogen). However, pretreatment with acetone resulted in statistically significantly increased kidney weight, inhibition of p-aminohippurate uptake, and increased levels of blood urea nitrogen after challenge with bromodichloromethane. With a challenge dose of dibromochloromethane, only blood urea nitrogen was significantly increased by acetone pretreatment. Acetone pretreatment of rats by gavage at doses of 196 and 392 mg/kg, prior to challenge with 1,1,2-trichloroethane, potentiated 1,1,2-trichloroethane-induced increased activity of plasma alanine aminotransferase (MacDonald et al. 1982a). However, higher pretreatment doses of acetone did not potentiate the toxicity and may have decreased the severity. Pretreatment of rats with acetone (392 mg/kg) followed by a challenge dose of ^{14}C-1,1,2-trichloroethane did not increase covalent binding of radioactivity to microsomal proteins but resulted in a greater decline in the content of reduced glutathione. When ^{14}C-trichloroethane was added *in vitro*, covalent binding of the radiolabel statistically significantly increased in microsomes from rats treated with acetone, compared with control microsomes (MacDonald et al. 1982b). The *in vitro* covalent binding was inhibited 80% by the addition of reduced glutathione. It was suggested that acetone alters the bioactivation and the detoxication of 1,1,2-trichloroethane, but the exact mechanism is unclear.

Acetone also potentiated the hepatotoxicity of chlorinated alkenes. Inhalation exposure of rats to 10,000 ppm acetone vapor for 2 hours prior to or during concomitant inhalation exposure to 2,000 ppm 1,l -dichloroethene resulted in statistically significant increased activity of serum alpha-ketoglutarate transaminase, compared with that induced by l,l-dichloroethene alone (Jaeger et al. 1975). A biphasic pattern of potentiation of the liver toxicity induced by l,l-dichloroethene was observed in rats pretreated orally with acetone at several dose levels (Hewitt and Plaa 1983). At doses of 290 and 581 mg/kg acetone prior to challenge with 1,l-dichloroethene, statistically significantly increased activities of plasma alanine aminotransferase and ornithine carbamoyltransferase were observed, compared with water pretreated rats challenged with 1,l-dichloroethene. At higher pretreatment doses of acetone ($\geq$871 mg/kg), the effect on these parameters diminished and acetone

appeared to have a protective effect. Treatment of rats with l,l-dichloroethene did not result in any evidence of nephrotoxicity, but acetone pretreatment statistically significantly reduced the accumulation of tetraethylammonium ion in kidney slices. The biphasic pattern of potentiation/protection may be related to alterations in the rate and/or pattern of l,l-dichloroethene bioactivation, such as, bioactivation to reactive intermediates or decreased detoxication by decreasing hepatic glutathione levels at the potentiating doses of acetone.

Benzene. Although potentiation of benzene toxicity by acetone has not been specifically tested, microsomes from rats treated with acetone (3,922 mg/kg) for 1 or 2-days produced a ≤9-fold increase in the rate of NADPH-dependent oxidation of benzene and induced cytochrome P-450, in particular cytochrome P-450j (cytochrome P-450IIEl) (Johansson et al. 1988; Johansson and Ingelman-Sundberg 1988). Addition of inhibitors of P-450IIEl inhibited the oxidation of benzene in microsomes from acetone treated rats, providing further evidence that this form of cytochrome P-450 is involved. In addition, antibodies to rabbit cytochrome P-450LMeb (IIEl) and rat cytochrome P-450j (IIEl) inhibited the oxidation of benzene by 80-100% in microsomes prepared from rabbits and rats treated with acetone. In hepatocytes from rabbits given acetone (863 mg/kg/day) in drinking water for 7 days, immunoblot analysis identified three distinct cytochromes: P-450IIE1, P-450IA1, and P-450IA2 (Schnier et al. 1989). In bone marrow cells from the treated rabbits, P450IIEl and P-450IAl were identified. Quantitative analysis revealed that acetone treatment resulted in a 7.3-fold induction of P-450IIEl in liver and a 12.9-fold induction of P-450IIEl in bone marrow cells. Acetone slightly decreased the concentration of cytochrome P-450 reductase in bone marrow, and increased the ratio of P-450IIEl to reductase by 16.4 times and the ratio of P-450IAl to reductase by 2 times. Hepatic microsomes from acetone-treated rabbits were 4.8 times more active than control microsomes in benzene hydroxylation, an activity of P-450IIEl. Acetone-induced marrow microsomes were 9.4 times more active in benzene hydroxylation. Thus, the stimulation of benzene metabolism by acetone occurs by a mechanism similar to that of the stimulation of carbon tetrachloride metabolism by acetone. The results suggest that acetone may potentiate the toxicity of benzene, since bioactivation is required for the expression of hematotoxicity of benzene (Sammet al. 1979; Snyder et al. 1975). It should be noted that commercial acetone contains 30 ppm benzene (Union Carbide 1992).

Dichlorobenzene. Inhalation exposure of rats to acetone vapors at 4,785, 10,670, or 14,790 ppm for 4 hours increased the cytochrome P-450 contents and the activity of glutathione-S-transferase, with the greatest increases occurring at the 4,785 ppm level (Brondeau et al. 1989). When the rats were

challenged 18 hours later by inhalation exposure to 1,2-dichlorobenzene, the level of P-450 and the activity of glutathione-S-transferase was no different from that seen with acetone alone. However, acetone preexposure potentiated the liver toxicity of 1,2-dichlorobenzene at the lowest exposure, reduced it at 10,670 ppm, and suppressed it at 14,790 ppm. In mice exposed to 6,747, 8,910, or 14,345 ppm acetone for 4 hours, followed by a challenge by l,2-dichlorobenzene, acetone preexposure caused an interactive glucose-6-phosphatase response in the mediolobular area of the liver. It was suggested that, at low concentrations, acetone induces the microsomal enzymes that convert 1,2-dichlorobenzene to toxic intermediates. However, since the glutathione-S-transferase activity did not increase in rats preexposed to acetone and challenged with 1,2-dichlorobenzene, the diminished liver toxicity induced by 1,2-dichlorobenzene after preexposure to the higher concentrations cannot be explained by detoxification via enhanced glutathione conjugation. Instead, two microsomal enzymes may be involved, in which, at low concentrations of acetone, one (activating) enzyme is induced, but at higher concentrations concomitant induction of the second enzyme system could result in protection.

Ethanol. Acetone potentiated the central nervous system toxicity of ethanol in mice (Cunningham et al. 1989). Mice were pretreated with an intraperitoneal injection of acetone in corn oil at 581, 1,162, or 2,323 mg/kg, and 30 minutes later injected with 4,000 mg/kg ethanol. At 1,162 and 2,323 mg/kg, acetone statistically significantly prolonged the duration of the loss of righting reflex induced by ethanol. In mice given 2,323 mg/kg acetone prior to 2,000 mg/kg ethanol, the blood level of ethanol was statistically significantly higher at all time intervals measured, and acetone pretreatment significantly decreased the mean elimination rate of ethanol.

In vitro, acetone inhibited the activity of liver alcohol dehydrogenase, a reaction responsible for 90% of ethanol elimination. It was suggested that acetone produced a prolongation of the central nervous system toxicity of ethanol by reducing its elimination.

Other Ketones. The neurological and reproductive effects of coexposure to acetone and 2,5-hexanedione has been studied in animals. In rats exposed to 0.5% 2,5-hexanedione, 0.5% acetone (650 mg/kg/day), or to a combination of 0.5% 2,5-hexanedione and 0.5% acetone in drinking water for 6 weeks, peripheral motor nerve conduction velocity was measured weekly from the third week of dosing (Ladefoged et al. 1989). Acetone alone reduced the nerve conduction velocity compared with controls only at 6 weeks, while 2,5-hexanedione alone significantly reduced it from the third week on. The combination treatment resulted in a statistically significantly greater reduction than seen with

2,5-hexanedione alone on the fourth and sixth week. Acetone alone had no effect on balance time in the rotorod test, but balance time was statistically significantly reduced from the second week with the combination treatment, and the reduction was greater than that with 2,5-hexanedione alone from the fourth week on. In a similar dosing regimen for 7 weeks, coexposure to 2,5-hexanedione and acetone statistically significantly inhibited acquisition, but not performance of spatial learning, (assessed in the radial arm maze) above that seen with 2,5-hexanedione alone (Lam et al. 1991). Brain weights of rats exposed to 2,5-hexanedione alone or to the combination were significantly reduced, with greater reduction in the coexposed group. Both treatments reduced synaptosomal 5-hydroxytryptamine uptake rate, but the combination treatment did not reduce the uptake below that seen with 2,5-hexanedione alone. In a companion report of these treatment groups, there was no significant difference on the number and size of neurons in the cerebral cortex between rats treated with 2,5-hexanedione alone or rats coexposed to 2,5-hexanedione and acetone (Strange et al. 1991).

Acetone alone had no effect on indices of fertility in male rats but potentiated the reproductive toxicity of 2,5-hexanedione when coadministered, compared with that seen with 2,5-hexanedione alone (Larsen et al. 1991). The rats were exposed to drinking water containing 0.13%, 0.25%, or 0.5% 2,5-hexanedione or in combination with 0.5% acetone for 6 weeks. Fertility was assessed by mating the exposed males with nonexposed females. 2,5-Hexanedione alone or the combination had no effects on the number of matings. 2,5-Hexanedione alone at 0.5% statistically significantly decreased the number of pregnancies, the number of fetuses, and the testicular weight. The combination treatments further reduced all indices, and at 0.5% 2,5-hexanedione plus 0.5% acetone, complete infertility occurred. Morphological assessment of the testes revealed mild to moderate vacuolization, chromatin margination, epithelial disruption, multinucleated giant cells, and/or atrophy in rats exposed to 2,5-hexanedione alone after 6 weeks of treatment, and the combination increased the severity of these lesions. When assessed 10 weeks after the end of treatment, the lesions were still present.

The mechanism by which acetone potentiates or adds to the toxicity of 2,5-hexanedione in rats is not known, but coexposure of rabbits to 2,5-hexanedione and acetone altered the pharmacokinetic parameters of 2,5-hexanedione (Ladefoged and Perbellini 1986). The combined treatment decreased the body clearance of 2,5-hexanedione, compared to the clearance of 2,5-hexanedione alone.

In a neurobehavioral study in volunteers, 11 men and 11 women exposed to 237 ppm acetone, 12 men and 13 women exposed to 200 ppm 2-butanone (methyl ethyl ketone), and 8 men and 13 women

exposed simultaneously to acetone (125 ppm) and 2-butanone (100 ppm) for 4 hours were subjected to psychomotor tests (choice reaction time, visual vigilance, dual task, memory scanning), sensimotor tests (postural sway), and psychological tests (profile of mood states) (Dick et al. 1989). Acetone exposure alone produced small, but statistically significant changes in performances from controls in two measures of auditory tone discrimination (increase response time and increase false alarm) and hostility in men only. Neither 2-butanone alone or the combination of acetone and 2-butanone produced any statistically significant changes. Furthermore, no interactions between acetone and 2-butanone on the uptake or elimination of acetone or 2-butanone were found in the same human subjects (Brown et al. 1987). From this limited information, it appears that acetone and 2-butanone do not interact to produce neurological effects.

Styrene. Although no studies were located regarding interactions between acetone and styrene in the expression of toxic effects in animals, several studies have reported that coexposure to acetone and styrene produce different changes in the content or activity of biotransformation enzymes in the liver and lungs, compared with the changes seen with styrene alone (Elovaara et al. 1990, 1991; Vainio and Zitting 1978). However, in humans subjects exposed for 2 hours to 293 mg/m^3 styrene alone or to a mixture of 301 mg/m^3 styrene and 1,240 mg/m^3 (517 ppm) acetone, there was no indication that acetone alters the uptake, distribution, metabolism, or elimination of styrene (Wigaeus et al. 1984).

Nitrusamines. Acetone potentiated the hepatotoxicity of N-nitrosodimethylamine in rats pretreated by gavage with 2.5 mL/kg (1,961 mg/kg) acetone in water 24 hours prior to a challenge intraperitoneal dose of 75 mg/kg N-nitrosodimethylamine (Lorr et al. 1984). The acetone pretreatment doubled the plasma activity of alanine aminotransferase ($p<0.005$) and increased the extent and severity of liver necrosis and hemorrhage, compared with that seen with N-nitrosodimethylamine alone. Microsomes prepared from rats treated with N-nitrosodimethylamine had diminished N-nitrosodimethylamine-N-demethylase activity, compared with microsomes from untreated mice. The results indicate that N-nitrosodimethylamine N-demethylase, an activity associated with cytochrome P-450IIE1, is responsible for the activation of N-nitrosodimethylamine to a toxic intermediate, and that the induction of this enzyme by acetone potentiates the hepatotoxicity. Microsomes from mice given 2,614 mg/kg acetone increased the covalent binding of radioactivity from [^{14}C]-N-nitrosodimethylamine to microsomal DNA, RNA, and protein (Sipes et al. 1978). Microsomes from rats pretreated with acetone had a four-fold increased activity of N-nitrosodimethylamine demethylase and a six-fold increase in DNA methylation compared with control microsomes (Hong and Yang 1985). Several

studies have shown that acetone given to rats or mice enhances the microsomal activity of N-nitrosodimethylamine N-demethylase in a dose-related manner (Miller and Yang 1984; Patten et al. 1986; Sipes et al. 1973, 1978; Tu et al. 1983; Yoo et al. 1990), and this activity is associated with cytochrome P-450 (Miller and Yang 1984; Tu et al. 1983; Yoo et al. 1990), in particular cytochrome P-45OIIEl (Patten et al. 1986; Yoo et al. 1990). Acetone pretreatment of rats also enhanced the denitrosation of N-nitroso-dimethylamine in microsomes, and antibodies against cytochrome P-450IIEl inhibited this activity (Yoo et al. 1990). Similar results were obtained with N-nitrosodiethylamine deethylation and denitrosation. The rates of both types of reactions depended upon the concentration of the nitrosamine in the reaction mixture, leading to the conclusion that P-45OIIEl has a role in the metabolism of low concentrations of these nitrosamines, and that this form of the enzyme is important in the carcinogen activation.

In Ames assays, addition of acetone to the S-9 mix inhibited the mutagenicities of N-nitrosodimethylamine, N-nitrosodiethylamine, 6 derivative of N-nitrosopropylamine, and N-nitroso-2,6-dimethylmorpholine in *S. typhimurium* Tal00 at a concentration of $\leq$5.2 mg/0.l mL (52,000 mg/L) nitrosamines (Mori et al. 1985). Acetone also inhibited the metabolism of N-nitrosodimethylamine, N-nitrosomethyl (2-hydroxypropyl)amine, and N-nitrosomethyl (2-0xopropyl)amine *in vitro.* In contrast, another study found that the S-9 mix prepared from mice treated with acetone strongly enhanced the mutagenicity of N-nitrosodimethylamine in the Ames assay in *S. typhimurium* TA92, which was more sensitive to N-nitrosodimethylamine than TAl00 (Glatt et al. 1981). This assay used concentrations of the nitrosamine at $\leq$20 mM (1,491 mg/L). However, acetone did not enhance the mutagenicity in the host-mediated assay. The authors explained that *in vitro,* the activity of the dilute metabolizing system is limiting for the activity of N-nitrosodimethylamine, such that induction increases mutagenicity, whereas *in vivo,* N-nitrosodimethylamine is completely metabolized in both induced and noninduced animals. The reason for the different effects of acetone on the mutagenicity of nitrosamines in the studies by Mori et al. (1985) and Glatt et al. (1981) could be related to differences in the assay system (e.g., acetone added to medium versus acetone-induced S-9), to the difference in concentration of the nitrosamines, or to the different strains of *S. typhimurium.* Microsomes from rats pretreated with acetone increased the activity of N-nitrosodimethylamine demethylase and increased the mutagenicity of N-nitrosodimethylamine in Chinese hamster lung V79 cell cultures at low substrate concentrations (0.1 and 4 mM or 5.8 and 232 mg/L) compared with untreated microsomes (Yoo and Yang 1985). However, a slight decrease in mutagenic activity was found at a N-nitrosodimethylamine concentration

of 200 mM (11,616 mg/L). Acetone induced microsomes also enhanced the mutagenic activity of N-nitrosomethylethylamine, N-nitrosodiethylamine, and N-nitrosomethylbutylamine, but not N-nitrosomethylbenzylamine or N-nitrosomethylaniline. The findings that lower concentrations enhanced the mutagenicity of N-nitrosodimethylamine (Glatt et al. 1981; Yoo and Yang 1985) are consistent with the conclusions of Yoo et al. (1990) that cytochrome P-450IIEl is important in the activation of the carcinogen at low concentrations.

Acetonitrile. Acetone also potentiates the toxicity of acetonitrile. When rats were given a 1:l mixture of acetone plus acetonitrile by gavage, the acute LD_{50} was 3-4 times lower than the predicted LD_{50} for additive toxicity (Freeman and Hayes 1985). The LD_{50} values of these chemicals alone were 5,800 mg/kg for acetone and 4,050 mg/kg for acetonitrile, while the LD_{50} for the mixture was 1,160 mg/kg, compared with the predicted value of 4,770 mg/kg. However, deaths occurred later with the mixture than with either acetone or acetonitrile alone. Blood cyanide (a toxic metabolite of acetonitrile) levels were higher, but peaked at a later time, in the rats given the mixture than in those given acetonitrile alone. Administration of a second dose of acetone 30 hours after administration of the mixture protected the rats from lethality to a degree similar to that seen with a dose of sodium thiosulfate (an antidote used for cyanide poisoning). It was suggested that, initially, acetone competitively inhibits the metabolism of acetonitrile to cyanide but later induces an isoenzyme of cytochrome P-450 that catalyzes the metabolism of acetonitrile to cyanide, hence explaining the greater toxicity of the mixture seen at a later time. To test this hypothesis, the metabolism of acetonitrile by microsomes from rats treated with acetone at the same dose that potentiated the toxicity was compared with that by noninduced microsomes (Freeman and Hayes 1988). The metabolism of acetonitrile required oxygen and NADPH and was inhibited by known inhibitors of cytochrome P-450. Microsomes from acetone pretreated rats increased the V_{max}, while acetone added to the reaction mixture *in vitro* competitively inhibited the conversion of acetonitrile to cyanide. The *in vitro* metabolism of acetonitrile was competitively inhibited by ethanol, which also induces cytochrome P-450IIE1, by dimethyl sulfoxide, which inhibits cytochrome P-450IIEl-dependent metabolism of ethanol, and by aniline, a substrate for P-45011El. Thus, the mechanism for the potentiation of the toxicity of acetonitrile by acetone also appears to involve cytochrome P-450IIEl.

A case report describes a woman who was asymptomatic for 24 hours after ingesting an overdose of acetonitrile and acetone, but subsequently developed cardiovascular collapse, and profound acidosis, and eventually died (Boggild et al. 1990). It was suggested that acetone delayed the onset of

symptoms by initially inhibiting the metabolism of acetonitrile to cyanide, which is consistent with the mechanism proposed by Freeman and Hayes (1988).

Acetaminophen. Acetone has been reported to increase the hepatotoxicity of acetaminophen *in vitro* (Moldeus and Gergely 1980) and *in vivo* (Jeffery et al. 1991). The addition of acetone to phenobarbital-induced rat liver hepatocytes caused a three-fold increase in acetaminophen-glutathione conjugation due to enhanced cytochrome P-450-dependent activation of acetaminophen to a toxic metabolite (Moldeus and Gergely 1980). The addition of acetone to the reaction system also caused loss of hepatocyte viability, which was not seen when acetone or acetaminophen were excluded from the system. According to the suggested mechanism, acetone enhanced a cytochrome P-450-dependent activation of acetaminophen to a metabolite that conjugates with glutathione, thereby depleting hepatic glutathione stores, leading to accumulation of the reactive metabolite. In contrast, pretreatment of rats with 813 or 1,975 mg/kg acetone 18 hours and 1 hour prior to administration of acetaminophen resulted in an increased blood half-life of acetaminophen, a decreased rate constant for acetaminophen mercapturate formation, decreased acetaminophen sulfate formation, and decreased renal elimination of acetaminophen (Price and Jollow 1983). Acetone also decreased the incidence and severity of liver necrosis induced by acetaminophen. The authors suggested that acetone decreased the formation of an acetaminophen reactive metabolite. However, in mice pretreated orally with acetone at 1,900 mg/kg/day for 10 days and then given 600 mg/kg acetaminophen intraperitoneally 6 hours before sacrifice, a greater portion of the liver lobules with necrosis and hemorrhage was observed than when acetaminophen was administered alone (Jeffery et al. 1991). Acetone pretreatment followed by saline injection resulted in no hepatic lesions. When dimethylsulfoxide (DMSO), an inhibitor of cytochrome P-450IIE1, was incubated with microsomes prepared from the acetone-pretreated, acetaminophen-treated mice, a 91% inhibition of acetaminophen-glutathione conjugation was found compared to when DMSO was excluded from the incubation mixture. Presumably, the inhibition of glutathione conjugation by DMSO was due to inhibition of cytochrome P-45011El to form the active metabolite of acetaminophen. Activation of acetaminophen to a reactive metabolite, N-acetyl-*p*-benzoquinone imine, which can bind to tissue macromolecules leading to necrosis at high doses of acetaminophen, is known to be dependent on cytochrome P-450IIEl (Morgan et al. 1983; Raucy et al. 1989). N-acetyl-*p*-benzoquinone imine can also be detoxified via conjugation with glutathione. The addition of acetone to the reaction system enhances the formation of the glutathione conjugate in rat liver microsomes (Liu et al. 1991). These results support a mechanism whereby acetone enhances the cytochrome P-450IIEl-dependent conversion of acetaminophen to N-acetyl-*p*-benzoquinone imine,

which in turn conjugates with glutathione to deactivate it. Thus, acetone could decrease the toxicity of acetaminophen. However, if the dose of acetaminophen is high, leading to more N-acetyl-*p*-benzoquinone imine than can be handled by glutathione detoxification, glutathione is depleted and N-acetyl-*p*-benzoquinone imine accumulates. Thus, the induction of cytochrome P-45OIIEl by acetone to produce enough N-acetyl-*p*-benzoquinone imine from acetaminophen to deplete glutathione would result in an enhancement of acetaminophen-induced toxicity.

Miscellaneous Chemicals. 9,10-Dimethyl-1,2-benzanthracene (DMBA) in acetone was more effective as a carcinogen than DMBA in mineral oil when applied to the tongues of hamsters (Marefat and Shklar 1977). A dose of 581 mg/kg acetone prior to administration of N-(3,5-dichlorophenyl)succinimide (NDPS), a fungicide, enhanced the NDPS-induced increase in blood urea nitrogen and kidney weight, but had no effect on NDPS-induced changes in urine volume or content, organic ion uptake by kidney slices, or renal pathology (Lo et al. 1987). Lower doses of acetone were ineffective. Since NDPS requires bioactivation by cytochrome P-450-dependent microsomal enzymes in the liver before renal toxicity occurs, it appears that acetone potentiated the renal toxicity of NDPS by inducing a cytochrome P-450 capable of the bioactivation. Pretreatment of rats with acetone prior to administration of thiobenzamide enhanced the degree of liver necrosis and serum activity of alanine aminotransferase, while coadministration of acetone and thiobenzamide reduced the extent of liver damage (Chieli et al. 1990). In addition, liver microsomes from acetone treated rats statistically significantly increased the rate of thiobenzamide-S-oxidation, which was dependent on a cytochrome P-450 enzyme. Thiobenzamide competitively inhibited acetone monooxygenase activity, which is highly specific for P-45011El. The results indicated that pretreatment of rats with acetone induces P-450IIE1, leading to enhanced bioactivation of thiobenzamide to a reactive metabolite and enhanced thiobenzamide-induced liver damage. However, when acetone and thiobenzamide were administered together, competition for the enzyme may have led to less bioactivation of thiobenzamide, thereby affording the protective effect of acetone. Acetone appears to afford protection against other toxic effects of other chemicals. Pretreatment of rats with acetone produced complete protection against clonic tonic convulsions induced by isonicotinic acid and electroshock-induced convulsion (Kohli et al. 1967). Since the protective action of acetone was nonspecific, a biochemical mechanism did not seem likely.

Acetone also increased the toxicity of oxygen (Tindberg and Ingelman-Sundberg 1989) and chromate (Cr[VI]) (Mikalsen et al. 1991). Pretreatment of rats with acetone prior to oxygen exposure

potentiated the NADPH-dependent microsomal lipid peroxidation in the liver and lung and decreased the survival of the rats (Tindberg and Ingelman-Sundberg 1989). Oxygen also induced cytochrome P-450IIE1, indicating a role for cytochrome P-450IIEl in oxygen-mediated tissue toxicity. Coexposure of rats to acetone and sodium chromate (Cr[VI]) resulted in some macroscopic alterations in the liver (not otherwise described), whereas no liver toxicity was noted with chromate or acetone alone (Mikalsen et al. 1991). Cytochrome P-450IIEl exhibited high chromate reductase activity, and biochemical studies indicated that acetone caused the induction of microsomal Cr(V1) metabolism.

While the interactions discussed above involve the potentiation of the toxicity of other chemicals by acetone, acetone has been found to antagonize the toxicity of semicarbizide (Jenney and Pfeiffer 1958). In mice injected intraperitoneally with 168 mg/kg semicarbizide, 93% had convulsions and 91% died. Pretreatment with 4,000 mg/kg acetone orally reduced the percentage of the semicarbizide-induced convulsions and mortality to 0%. A dose of 1,800 mg/kg acetone reduced the percentage of mice convulsing to 31%, delayed the onset of convulsions by 286%, reduced the percentage that exhibited unmodified seizure from 98% to 40%, reduced the mortality to 12.5%, and delayed the time to death by 125%. The authors attributed the protective effect of acetone to the presence of the keto group.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to acetone than will most persons exposed to the same level of acetone in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the preexisting compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, “Populations With Potentially High Exposure.”

Several lines of evidence from studies in animals indicate that sex differences exist in the susceptibility to effects caused by acetone. Male rats were more susceptible than female rats to acetone’s

hematological, hepatic, and renal effects, and effects on reproductive organs (American Biogenics Corp 1986; NTP 1991). While results in animals cannot always be extrapolated to humans, it is possible that men may be more susceptible than women to the hematological, hepatic, renal, and reproductive effects of acetone. Furthermore, acetone may exacerbate preexisting hematological, liver, kidney, or reproductive disorders in humans.

In a lethality study among newborn rats, 14-day-old rats, and adult rats, susceptibility to the lethal effects of acetone generally decreased with increasing maturity (Kimura et al. 1971). Humans may have the same order of susceptibility.

Pregnant rats exposed to acetone by inhalation during gestation had reduced body weights (NTP 1991), while nonpregnant rats exposed to a higher concentration for a longer duration did not show any effects on body weight (Goldberg et al. 1964). Pregnant rats also had lower plasma and liver levels of acetol, the first intermediate in the overall metabolism of acetone, than virgin rats (Peinado et al. 1986), suggesting differences in the rate of acetone metabolism. It is possible that the condition of pregnancy made these rats more susceptible to body weight changes, and this susceptibility might apply to humans.

The role of acetone in fasting and diabetes is complicated and not well understood (Reichard et al. 1979; 1986). Acetone is produced endogenously and, as demonstrated in humans, more acetone is produced endogenously by fasting, which can result in ketosis (Reichard et al. 1979). This implies that people on diets exposed to exogenous acetone will have a higher body burden of acetone than nondieters exposed to the same amount of exogenous acetone, perhaps making them more susceptible to any possible adverse effects. Acetone exposure of rats resulted in a reduced insulin-stimulated glucose oxidation rate, and the reduction was greater in fasted rats than in fed rats, indicating that the insulin resistance indigenous to fasting may be attributed in part to metabolic influences of acetone (Skutches et al. 1990). This implies that people on diets may have a diminished capacity to utilize glucose, and exposure to acetone may reduce the capacity further.

Diabetics may also be more susceptible to the effects of acetone. Acetone-induced insulin resistance (Skutches et al. 1990) might also result in greater hyperglycemia in diabetics. Patients with diabetic ketoacidosis have higher plasma levels of endogenous acetone (Reichard et al. 1986), and exposure to exogenous acetone may increase the levels further. Similar results were found in rats. Diabetic rats

had higher plasma acetone levels than nondiabetic rats after treatment with the same doses of acetone, due to the higher endogenous level of acetone in the diabetic rats and differences in the metabolism of acetone to isopropyl alcohol (Lewis et al. 1984). Diabetic rats were also less able to oxidize acetone than nondiabetic rats (Price and Rittenberg 1950).

2.8 METHODS FOR REDUCING TOXIC EFFECTS

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

2.8.1 Reducing Peak Absorption Following Exposure

Since acetone is irritating to mucous membranes of the respiratory system and eyes, people exposed occupationally wear protective clothing, goggles, and respirators (Stutz and Janusz 1988). If exposure has occurred and symptoms of narcosis are present, the victim is removed from the contaminated area, clothing is removed and isolated, the skin is washed with soapy water, oxygen is administered, and eyes are thoroughly flushed with water. In the case of ingestion of acetone, activated charcoal is given. Although induction of emesis by administration of syrup of ipecac is sometimes recommended in the case of ketones in general (Stutz and Janusz 1988), this may be contraindicated in the case of acetone ingestion because of the possibility of pulmonary aspiration, which increases for substances with high volatility and low viscosity (Goldfrank et al. 1990). Gastric lavage has been used to treat a patient who ingested acetone (Sakata et al. 1989), but the possibility of aspiration also exists for this method (Goldfrank et al. 1990).

2.8.2 Reducing Body Burden

Following inhalation or oral exposure, acetone is eliminated within about l-3 days in humans (DiVincenzo et al. 1973; Matsushita et al. 1969a, 1969b; Ramu et al. 1978; Sakata et al. 1989). Acetone does not accumulate in any tissue and its metabolites do not appear to be toxic or retained (Wigaeus et al. 1982). To reduce the body burden of acetone, a cathartic, such as magnesium sulfate

in water, is administered (Stutz and Janusz 1988). In a case of isopropyl alcohol poisoning (acetone is a major metabolite of isopropyl alcohol), hemodialysis has been used successfully to enhance elimination of both isopropyl alcohol and acetone (Rosansky 1982).

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of the narcotic effects of acetone is not known, but as a solvent, acetone may interfere with the composition of the membranes, altering their permeability to ions (Adams and Bayliss 1968). Systemically, acetone is moderately toxic to the liver, and produces hematological effects. The mechanism by which acetone produces these effects is unknown. The renal toxicity may be due to the metabolite, formate, which is known to be nephrotoxic (NTP 1991), and is excreted by the kidneys (Hallier et al. 1981). Furthermore, the renal toxicity, which appears to be specific for male rats, may involve $\alpha_{2\mu}$-globulin syndrome, as hyaline droplet formation was associated with the nephropathy observed in male rats in the American Biogenics Corp. (1986) study. Acetone also causes reproductive effects in male rats, and is fetotoxic. Although the exact mechanism for many of the effects of acetone is not known, distribution studies in mice indicate that acetone and metabolites are found in all of the target organs (Wigaeus et al. 1982). Acetone and some of its metabolites were also transferred to rat fetuses after the dams were exposed to acetone (Peinado et al. 1986). The metabolites of acetone are gluconeogenic precursors and most do not appear to be the toxic. Therefore, acetone itself appears to be a toxic agent, and increasing the metabolism of acetone would appear to be the best method for interfering with the mechanism of action. However, acetone induces its own metabolism by inducing cytochrome P-450IIEl (Johansson et al. 1986; Puccini et al. 1990). The first and second steps of the metabolism of acetone are dependent on cytochrome P-45OIIEl (Casazza et al. 1984; Johansson et al. 1986; Koop and Casazza 1985; Puccini et al. 1990). Since ethanol also induces this particular form of P-450IIEl (Johansson et al. 1988; Puccini et al. 1990), the metabolism of acetone might be increased by administering ethanol, although this may competitively slow acetone metabolism, at first, and induce cytochrome P-450IIEl only after a lag of several hours. In healthy men who fasted for 12 hours, the breath acetone levels ranged from 0.96 to 1.7 ppm (Jones 1987). Fasting for 36 hours resulted in average acetone breath levels of 14-66 ppm. In fasting men who ingested 0.25 g/kg of ethanol, the breath acetone levels decreased by 40% after a 12-hour fast and by 18% after a 36-hour fast (Jones 1988). However, since acetone potentiates the toxicity of other chemicals by inducing cytochrome P-45OIIE1, which enhances the metabolism of the chemicals to reactive intermediates (see Section 2.6), further increasing the cytochrome P-450IIEl levels might be

counterproductive in cases of exposure to acetone followed by exposure to the other chemicals. Furthermore, acetone potentiates the central nervous system toxicity of ethanol by reducing the activity of alcohol dehydrogenase, which is responsible for 90% of ethanol elimination (Cunningham et al. 1989).

2.9 ADEQUACY OF THE DATABASE

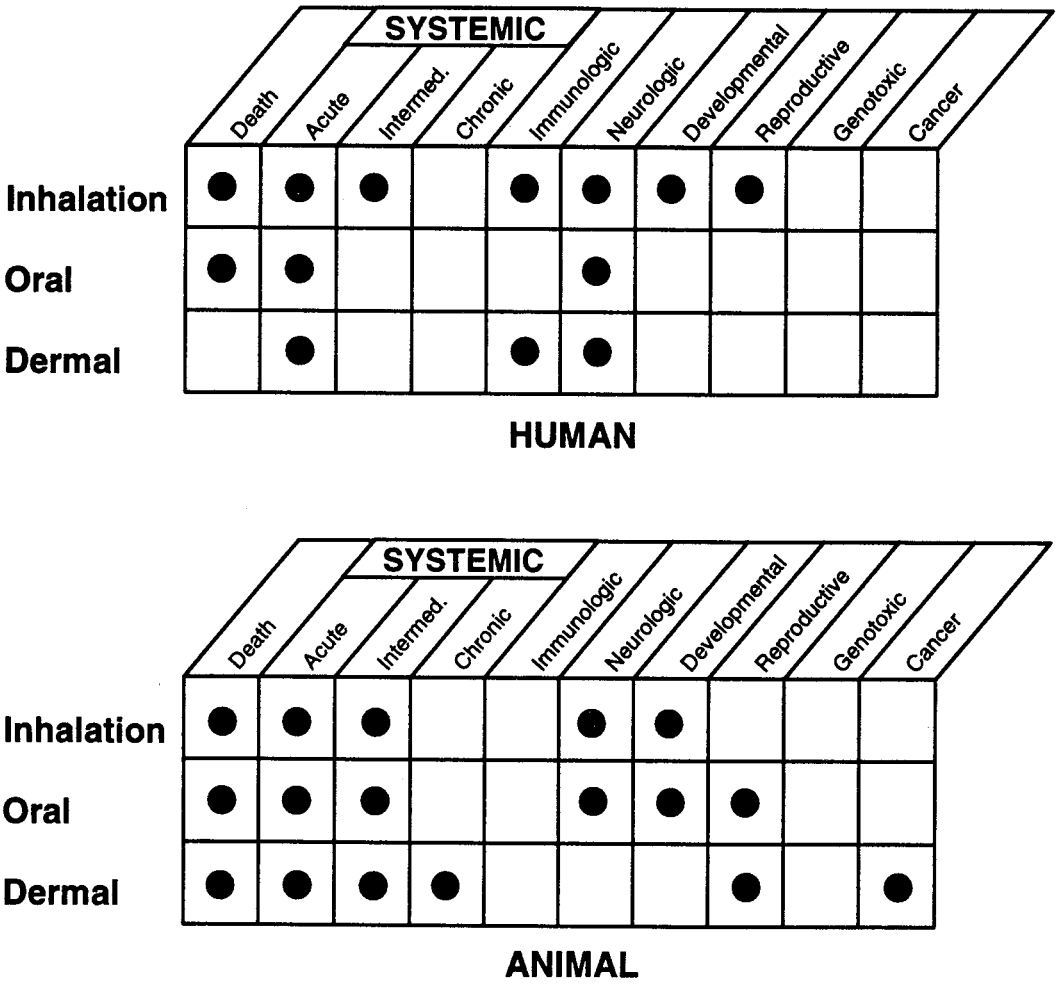
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of acetone is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of acetone.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of Acetone

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to acetone are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of acetone. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as “data needs.” A data need, as defined in ATSDR’s Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

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



f39023-1

As seen from Figure 2-4, data exist for inhalation exposure of humans for death, for systemic effects of acute- and intermediate-duration exposure, and for immunological, neurological, developmental, and reproductive effects. The data for systemic, neurological, immunological, and neurological effects were derived from medical evaluations of workers after a single day exposure, from case reports, and from experimental studies of humans exposed for acute- and intermediate-durations. The systemic effects include respiratory irritation, cardiovascular effects, gastrointestinal effects, and hematological effects, with no indications of hepatic or renal effects. Possible immunological effects consisted of increased white blood cell counts and decreased phagocytic activity of neutrophils. Neurological effects consisted of subjective symptoms, coma, and some behavioral effects. Reproductive and development effects consisted of shortened menstrual periods of women in an experimental study. An epidemiological study of pregnancy outcome among female laboratory workers who handle solvents found no effects, but an unreliable study of pregnancy complications in Russian women factory workers reported reproductive and developmental effects. Information in humans after oral exposure was derived from case reports of intentional or accidental ingestion. Effects included erosions in the buccal cavity, development of diabetes-like symptoms, and coma, and other neurological effects. Effects of dermal/ocular exposure of humans consisted of eye irritation, degenerative changes in the epidermis, and the development of contact dermatitis in a sensitized woman. In addition, patients exposed by inhalation and/or dermally from applications of casts using acetone as a setting agent developed increased pulse rate, vomiting and nausea, and neurological effects, including coma.

For animals exposed by inhalation, data exist for death, systemic effects of acute- and intermediate-duration exposure, and neurological, developmental, and reproductive effects. Systemic effects consisted of respiratory irritation, hepatic effects, renal effects, and body weight changes. Neurological effects consisted of narcosis, coma, and behavioral effects. Fetotoxicity, but no reproductive effects, were found in a developmental study. For oral exposure, data in animals were available for death (acute), systemic effects of acute- and intermediate-duration exposure, and neurological, reproductive, and developmental effects. Systemic effects included respiratory (enzyme induction), hematological, hepatic, and renal effects, and reduced insulin-stimulated glucose oxidation and body weight changes. No cardiovascular, gastrointestinal (other than enzyme induction), musculoskeletal, or dermal/ocular effects were found. Neurological effects consisted of narcotic effects and reduced nerve conduction velocity. Reproductive effects were found in male rats, and fetotoxicity was found in a developmental study. Effects of dermal/ocular exposure consisted of amyloidosis in the heart, liver, kidney, pancreas, and adrenals of mice exposed dermally, eye irritation and cornea1 burns and necrosis, skin irritation,

and cataract development due to dermal exposure. Mice used as acetone solvent controls in skin painting studies did not develop any acetone-related neoplastic or nonneoplastic lesions after comprehensive histological examination. Acetone was negative as a tumor initiator or promotor in skin painting studies.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. Acute inhalation studies in volunteers (Matsushita et al. 1969a, 1969b; Nelson et al. 1943) and on-site medical evaluations of workers on a single work day (Raleigh and McGee et al. 1972; Ross 1973) have found that acetone is irritating to the nose, throat, trachea, lungs, and eyes. Acute experimental studies in humans also found hematological effects, which might also indicate immunological effects (Matsushita et al. 1969a, 1969b) and neurological and neurobehavioral effects (Dick et al. 1989; Haggard et al. 1944; Matsushita et al. 1969a, 1969b; Seeber and Kieswetter 1991; Seeber et al. 1992). Case reports of patients exposed to acetone vapors by inhalation and/or dermally during and after application of hip casts have found cardiovascular effects (increased pulse rates), gastrointestinal effects (vomiting of blood, hemorrhage), and neurological effects (lethargy, headache, listlessness, mystagmus, dizziness, coma, collapse) (Chatterton and Elliot 1946; Fitzpatrick and Claire 1947; Harris and Jackson 1952; Hift and Pate1 1961; Pomerantz 1950; Renshaw and Mitchell 1956; Strong 1984). No indication that the liver and kidney were target organs, based on clinical chemistry parameters, was found in humans exposed under laboratory conditions (DiVincenzo et al. 1973). Information on effects of acute oral exposure in humans was derived from case reports of accidental or intentional ingestion of acetone and indicate that ingestion causes coma (Gamis and Wasserman 1988; Gitelson et al. 1966; Ramu et al. 1978; Sakata et al. 1989), erosions in the buccal cavity, and possible diabetes-like symptoms (Gitelson et al. 1966). Direct application of acetone to the skin of humans resulted in skin irritation and degenerative changes in the epidermis (Lupulescu et al. 1972, 1973; Lupulescu and Birmingham 1975, 1976), and a case of contact dermatitis was reported (Tosti et al. 1988). Acute inhalation studies in animals have provided LC_{50} values for rats (Pozzani et al. 1959) and have identified the respiratory system (irritation) in mice and guinea pigs (Kane et al. 1980; Specht et al. 1939), liver in mice, guinea pigs, and rats (NTP 1988; Specht et al. 1939; Vainio and Zitting 1978), and kidney in guinea pigs (Specht et al. 1939) as possible target organs. The heart and stomach did not appear to be target organs, and the kidney effects in guinea pigs were found at lethal concentrations (Specht et al. 1939). For acute oral exposure in animals, LD_{50} values are available for rats (Freeman and Hayes 1985; Kimura et al. 1971; Pozzani et al. 1959; Smyth et al.

1962), for mice (Tanii et al. 1986), and guinea pigs (Striegel and Carpenter 1961). Oral doses associated with death were also available for rabbits (Walton et al. 1928) and dogs (Albertoni 1884). The systemic effects of acute oral exposure found in animals were enzyme induction in the respiratory system of hamsters (Ueng et al. 1991) and rabbits (Ding and Coon 1990) in the duodenum and jejunum of rats (Carriere et al. 1992), in the bone marrow of rabbits (Schnier et al. 1989), in the liver of rats, mice, rabbits, guinea pigs, and hamsters (see Section 2.2.2.2), and in the kidneys of hamsters (Menacagli et al. 1991; Ueng et al. 1992) and rats (Hong et al. 1987), increased liver weight in mice and bone marrow hypoplasia in rats (Dietz et al. 1991; NTP 1991) kidney effects in rats (Brown and Hewitt 1984), and reduced insulin-stimulated glucose oxidation in adipose tissue in rats (Skutches et al. 1990). Acute dermal exposure of animals produced increased DNA synthesis in the skin, indicative of irritation, in mice (Iversen et al. 1988), and ocular exposure caused cornea1 bums and necrosis in rabbits and guinea pigs (Bolkova and Cejkova 1983; Carpenter and Smyth 1946; Smyth et al. 1962). Acetone does not appear to be very toxic by the dermal route, as attempts to determine LD_{50} values for rabbits and guinea pigs found no deaths at the highest dermally applied concentrations (Roudabush et al. 1965; Smyth et al. 1962). The acute inhalation study of Specht et al. (1939) was conducted at lethal concentrations. An acute inhalation MRL of 26 ppm was derived based on neurobehavioral effects in humans. Most of the acute inhalation and oral studies in animals were designed to study enzyme induction. Comprehensive histological examination was performed in the high dose and control animals in the 14-day drinking water study in rats and mice exposed at several dose levels (Dietz et al. 1991; NTP 1991). An acute oral MRL was not derived because NOAEL and LOAEL values in rats or mice in the acute-duration drinking water studies (Dietz et al. 1991; NTP 1991; Skutches et al. 1990) were close to or fell within the range of LD_{50} values for rats exposed by gavage (Freeman and Hayes 1985; Kimura et al. 1971). Acute-duration inhalation and oral studies conducted at several exposure levels in rats and mice that perform clinical tests and comprehensive histological examination of all dose groups would provide valuable information on dose-response relationships and better characterize target organs, which might serve as bases for the development of MRLs. This information is important because there are populations surrounding hazardous waste sites that might be exposed to acetone for brief periods.

Intermediate-Duration Exposure. The only information located regarding systemic effects in humans after intermediate-duration inhalation exposure was an experimental study in volunteers exposed intermittently to acetone at concentrations $\leq$1,250 ppm for $\leq$7.5 hours and $\leq$5 or 6 weeks in a complex protocol (Stewart 1975). Throat irritation was reported, but pulmonary function testing,

electrocardiography, clinical chemistry and urinalysis determinations for liver and kidney damage, and hematology did not reveal any abnormalities. No studies were located regarding effects in humans after intermediate-duration oral or dermal exposure to acetone. An intermediate-duration inhalation study in rats found no histological or clinical evidence of effects on lungs, hearts, kidneys, or livers (Bruckner and Peterson 1981b), but histological examination was not comprehensive. An intermediate inhalation MRL of 13 ppm was derived based on neurological effects in humans. An intermediateduration drinking water study found increased liver weight in mice and hematological effects (macrocytic anemia), increased liver weight, and kidney effects (nephropathy) in rats (Dietz et al. 1991; NTP 1991). An intermediate-duration gavage study in rats found clinical evidence of liver effects, hematological effects, and nephropathy (American Biogenics Corp. 1986). The renal effects seen in these studies appeared to be specific for male rats and may be related to $\alpha_{2\mu}$-globulin syndrome, since hyaline droplet formation was observed in the American Biogenics Corp. (1986) study, but not the NTP (1991) study. No other systemic target organs were identified by comprehensive histological examination. An intermediate-duration oral MRL of 2 mg/kg/day was derived based on the NOAEL for macrocytic anemia in rats in the 13-week drinking water study (Dietz et al. 1991; NTP 1991). Intermediate-duration dermal exposure of animals resulted in moderate hyperplasia of the epidermis of mice (Iversen et al. 1981), mild erythema and transient weight loss in guinea pigs (Taylor et al. 1993), cataracts in the eyes of guinea pigs (Rengstorff et al. 1972), and amyloidosis in the heart, liver, kidney, skin, pancreas, and adrenals of mice (Barr-Nea and Wolman 1977). Intermediate-duration ocular exposure of rabbits resulted in uveal melanocytic hyperplasia (Pe'er et al. 1992). An intermediate-duration inhalation study in rats and mice that is designed to establish dose-response data for noncancer end points would also provide dose-response relationships and identify target organs useful for MRL derivation and fill this data gap. An intermediate-duration drinking water study in rats conducted at lower exposure levels than those used in the NTP (1991) study might provide information on the threshold for anemia and nephropathy. Furthermore, a study designed to confirm whether the acetone-induced nephrotoxicity is related to $\alpha_{2\mu}$-globulin syndrome would aid in the assessment of the relevance of the renal effects to human health. Examination of workers who handle liquid acetone might provide information on the relevance to humans of the cataract formation and amyloidosis seen in animals. This information is important because there are populations surrounding hazardous waste sites that might be exposed to acetone for similar durations.

Chronic-Duration Exposure and Cancer. A retrospective mortality study of workers exposed to acetone found no significant excess risk of death from any cause (all causes, malignant neoplasm,

circulatory system disease, ischemic heart disease) (Ott et al. 1983a, 1983b). Furthermore, a health evaluation survey of active employees found no evidence of hematological or liver effects (Ott et al. 1983a, 1983c). No studies were located regarding systemic effects in humans after oral or dermal exposure to acetone or in animals after inhalation or oral exposure for chronic durations. The only information regarding systemic effects in animals after chronic-duration exposure to acetone is that female mice used as acetone solvent controls in skin painting studies did not develop any acetone-related nonneoplastic lesions after comprehensive histological examination (Ward et al. 1986) and that chronic dermal of exposure of mice resulted in low incidences of hyperplasia, dermatitis, and hyperkeratosis (DePass et al. 1989). A chronic inhalation MRL of 13 ppm was derived based on meurological effects in humans in an intermediate-duration study. The lack of data regarding systemic effects after oral exposure precludes the derivation of an oral MRL. The conduct of chronic studies by these routes in rats and mice would provide information on the dose-response relationships and identify target organs of chronic inhalation and oral exposure to acetone. This information is important because there are populations surrounding hazardous waste sites that might be exposed to acetone for long periods of time.

A retrospective mortality study of workers exposed to acetone found no significant excess risk of death from any cause, including malignant neoplasm (Ott et al. 1983a, 1983b). No studies were located regarding cancer in humans after oral or dermal exposure to acetone, or in animals after inhalation or oral exposure. Mice used as acetone solvent controls in skin painting studies did not develop any acetone-related neoplastic lesions after comprehensive histological examination (Ward et al. 1986) or skin tumors (DePass et al. 1989; Van Duuren et al. 1978). Acetone was negative as a tumor initiator (Roe et al. 1972) and as a tumor promoter for 7,12-dimethylbenz[a]anthracene (Roe et al. 1972; Van Duuren et al. 1971; Weiss et al. 1986). Following dermal absorption, acetone is probably widely distributed throughout the body, as occurs after pulmonary absorption (Wigaeus et al. 1982). However, it is not possible to predict that acetone would not be carcinogenic after inhalation or oral exposure, because quantitative data regarding dermal absorption were not located. Genotoxicity studies indicate that acetone may be weakly genotoxic (see below). Chronic inhalation and oral studies in rats and mice designed to establish dose-response data for noncancer end points would also provide information on the potential for acetone to cause cancer.

Genotoxicity. No studies were located regarding genotoxicity in humans or animals after inhalation, oral, or dermal exposure. *In vivo* genotoxicity studies were conducted by the intraperitoneal route for

micronuclei formation in Chinese hamsters (Basler 1986) and for cell transformation in fetal cells from pregnant hamsters (Quarles et al. 1979a, 1979b) with negative results. In addition, tests for gene mutation in silk worms by an unspecified route were negative (Kawachi et al. 1980). Numerous studies were conducted *in vitro*. Mostly negative results were obtained in bacterial (De Flora 1981; De Flora et al. 1984; De Marini et al. 1991; Ishidate et al. 1984; Kawachi et al. 1980; Kubinski et al. 1981; McCann et al. 1975; Rossman et al. 1991; Yamauchi 1985) and yeast (Abbandandolo et al. 1980; Albertini 1991) assays and in plant seeds (Gichner and Veleminsky 1987) with or without metabolic activation, but some results were positive in *E. coli* when acetone was in the triplet state (Menck et al. 1986; Rahn et al. 1974) and in yeast for aneuploidy (Zimmermann 1983; Zimmermann et al. 1984, 1985) and for mitotic chromosome malsegregation (Albertini 1991) without metabolic activation. Mostly negative results were obtained in assays for cell transformation, chromosomal aberrations, sister chromatid exchange, colony formation inhibition, and gene mutation in cultured animal cells (Amacher et al. 1980; Chen et al. 1984; DiPaolo et al. 1969; Freeman et al. 1973; Kawachi et al. 1980; Mishra et al. 1978; Pienta 1980; Rhim et al. 1974; Tates and Kriek 1981), and for sister chromatid exchange and unscheduled DNA synthesis in cultured human fibroblasts and skin epithelial cells (Abe and Sasaki 1982; Kawachi et al. 1980; Lake et al. 1978). However, some positive results were obtained for chromosomal aberrations in Chinese hamster fibroblasts (Ishidate et al. 1984) and hamster lung fibroblasts (Kawachi et al. 1980), for inhibition of metabolic cooperation in Chinese hamster cells (Chen et al. 1984), and for chromosome malsegregation in porcine brain tubulin (Albertini et al. 1988). Acetone did not promote the transforming activity initiated by nine known genotoxic and carcinogenic chemicals (Sakai and Sato 1989). The mostly negative results in bacteria and cultured animal cells and the negative results in human fibroblasts and skin epithelial cells indicate that acetone poses little threat for genotoxicity in humans. However, peripheral lymphocytes, fibroblasts, and skin epithelial cells from workers exposed to acetone could be examined for chromosomal aberrations to confirm this hypothesis.

Reproductive Toxicity. Information regarding reproductive effects in humans after inhalation exposure is limited to the report of premature menstrual periods by 3 of 4 women exposed to 1,000 ppm acetone for 7.5 hours (Stewart et al. 1975), the lack of a statistically significant increased incidence of miscarriage in female laboratory workers exposed to a variety of solvents, including acetone (Axelsson et al. 1984) and an unreliable report of pregnancy complications of Russian women factory workers (Nizyaeva 1982). No studies were located regarding reproductive effects in humans after oral or dermal exposure to acetone. Information regarding reproductive effects in animals after

inhalation exposure is also limited. In an inhalation developmental study in rats and mice, no effects were found on the number of implants/litter, percent live pups/litter, or mean percent resorptions/litter (NTP 1988). No studies were located regarding reproductive effects in male animals, histological effects on reproductive organs of male or female animals, or the reproductive outcomes and other indices of reproductive toxicity in animals after inhalation exposure to acetone. Reproductive effects (reduced reproductive index and increased duration of gestation) were found in pregnant mice exposed orally to 3,500 mg/kg/day during gestation (EHRT 1987). In a 6-week drinking water study in male Wistar rats, no effects were found on successful mating to untreated females, number of pregnancies, number of fetuses, testicular weight, seminiferous tubule diameter, and testicular lesions (Larsen et al. 1991). However, male Sprague-Dawley rats had statistically significantly decreased sperm motility, caudal weight and epididymal weight, and increased incidences of abnormal sperm, but no histopathological testicular lesions in a 13-week drinking water study (NTP 1991). Vaginal cytology examinations of the female rats revealed no effects, and similar evaluations of male and female mice revealed no effects. No indication that dermal exposure of female mice results in histopathological effects in reproductive organs was found in an analysis of female SENCAR mice used as acetone controls in a skin painting study of formaldehyde (Ward et al. 1986). An inhalation distribution study in male mice showed that acetone is distributed to the testes and vas deferens (Wigaeus et al. 1982), and the 13-week oral study showed effects on the male rat reproduction organs. Acetone is widely distributed throughout the body regardless of route of exposure and species. Therefore, it is reasonable that male rats (and perhaps male mice) exposed to acetone by inhalation for 13 weeks might have effects on reproductive organs, but the concentration of acetone that would cause such effects cannot be predicted. Therefore, reproductive organ pathology should be examined in the suggested intermediate-duration inhalation study. The reproductive organs of female rats and mice could also be examined in the intermediate-duration inhalation study to confirm the lack of effects in the existing oral study. A multi-generation study conducted by the oral route would clarify whether the reproductive effects observed in male rats in the existing 13-week drinking water study would affect reproductive outcomes and other indices of reproduction. If the proposed intermediate-duration inhalation study showed reproductive organ pathology, a similar multigeneration study by the inhalation route might be warranted.

Developmental Toxicity. Information regarding developmental effects in humans after inhalation exposure is limited to a report that found no statistically significant increased incidence of miscarriage, perinatal death rate, or malformations of offspring in female laboratory workers exposed to a variety of

solvents, including acetone (Axelsson et al. 1984) and an unreliable report of fetal death and reduced birth weight and length of neonates in Russian women factory workers exposed to acetone (Nizyaeva 1982). No studies were located regarding developmental effects in humans after oral or dermal exposure to acetone. Developmental effects have been found in animals after inhalation and oral exposure. Decreased mean fetal body weight occurred at maternally toxic doses in rats exposed by inhalation during gestation (NTP 1988). Significantly increased incidence of late resorption, decreased fetal weight, and significantly increased incidence of reduced sternebral ossification occurred at maternally toxic doses in mice exposed by inhalation during gestation (NTP 1988). In mice exposed orally during gestation, reduced postnatal pup survival and reduced average weight of each live pup/litter on postpartum day 0 occurred at maternally toxic doses (EHRT 1987). Fetuses or pups were not examined for internal malformations or skeletal anomalies. Therefore, a more conventional oral developmental toxicity study in mice would help to determine whether acetone causes fetal malformations or skeletal anomalies. Developmental studies were not conducted in rats by the oral route, but while it is reasonable to expect that fetotoxicity would occur, it is not possible to predict the dose that would cause fetotoxicity in rats. An oral developmental study in rats would provide this information. No studies were located regarding developmental effects in animals after dermal exposure to acetone. Acetone can undergo transplacental transfer (Peinado et al. 1986). While it appears that acetone is absorbed after dermal exposure, quantitative data were not available. If enough acetone is absorbed dermally, then fetotoxicity by this route would also be expected. A dermal developmental study might confirm or refute this possibility. Acetone has been tested in attempts to develop *in vitro* methods for assessing developmental toxicity in postimplantation rat embryos (Kitchin and Ebron 1984; Schmid 1985) and in mouse embryo limb buds (Guntakatta et al. 1984) with inconclusive results. Further *in vitro* studies could be conducted to resolve the inconsistencies, but such studies would be useful only for preliminary screening purposes and would not substitute for developmental studies in animals administered acetone by environmentally relevant routes.

Immunotoxicity. Information regarding immunological effects in humans after exposure to acetone is limited. Significantly increased white blood cell counts, increased eosinophil counts, and decreased phagocytic activity of neutrophils were found in volunteers exposed by inhalation (Matsushita et al. 1969a, 1969b), but a battery of immune function tests has not been performed. A case report of a laboratory technician described the development of acute contact dermatitis from handling acetone 2 years after being treated with squaric acid dibutyl ester in acetone for patchy alopecia areata on her scalp (Tosti et al. 1988). This acetone sensitization is considered a rare complication of sensitizing

therapies for alopecia areata. No studies were located regarding immunological effects in humans after oral exposure or in animals after inhalation, oral, or dermal exposure to acetone. A study performing a battery of immune function tests would clarify whether acetone is an immunotoxicant.

Neurotoxicity. Exposure to acetone by the inhalation and oral routes has resulted in neurological effects, related to the narcotic effects of acetone, in both humans and animals. Acetone can cause coma and other neurological effects in humans after inhalation and/or dermal exposure (Chatter-ton and Elliott 1946; Fitzpatrick and Claire 1947; Harris and Jackson 1952; Hift and Pate1 1961; Pomerantz 1950; Renshaw and Mitchell 1956; Ross 1973; Strong 1944) or oral exposure (Gamis and Wasserman 1988; Ramu et al. 1978; Sakata et al. 1989) if exposure levels or doses are high enough. Neurological effects were commonly experienced by workers and volunteers exposed by inhalation to acetone and include headache, lightheadedness, dizziness, unsteadiness, and confusion (Raleigh and McGee 1972; Ross 1973). Neurobehavioral tests conducted in some of these workers were negative (Raleigh and McGee et al. 1972). Neurological and behavioral effects have also been observed in volunteers exposed by inhalation (Dick et al. 1989; Haggard et al. 1944; Matsushita et al. 1969a, 1969b; Seeber and Kieswetter 1991; Seeber et al. 1992; Stewart et al. 1975). Neurobehavioral effects, indicative of narcosis, have been observed in rats (Bruckner and Peterson 1981a; Garcia et al. 1978; Geller et al. 1979b; Goldberg et al. 1964; Haggard et al. 1944), mice (DeCeaurriz et al. 1984; Glowa and Dews 1987; Mashbitz et al. 1936), and baboons (Geller et al. 1979a) exposed by inhalation. Acetone was also neurotoxic in rats after oral exposure, producing prostration (Freeman and Hayes 1985), reduction in nerve conduction velocity (Ladefoged et al. 1989), and excessive salivation (American Biogenics Corp. 1986). Oral exposure to acetone caused prostration in mice (EHRT 1987), weakness, depression, and unconsciousness in rabbits (Walton et al. 1928), and incoordination, staggering, falling, tremors, delirium, prostration, and coma in dogs (Albertoni 1884). No studies were located regarding neurological effects in animals after dermal exposure to acetone. There is no reason to suspect that the effects are route- or species-specific. Acetone is widely distributed throughout the body after absorption, and its presence in the brain of mice after inhalation exposure has been demonstrated (Wigaeus et al. 1982). If enough acetone is absorbed dermally, neurological effects could occur; however, no studies that applied acetone to the skin of animals (Iversen et al. 1981, 1988; Rengstorff et al. 1972, 1976; Ward et al. 1986) described any neurological signs of toxicity.

Epidemiological and Human Dosimetry Studies. A retrospective mortality study of workers exposed to acetone found no significant excess risk of death from any cause (all causes, malignant

neoplasm, circulatory system disease, ischemic heart disease) (Ott et al. 1983a, 1983b). Furthermore, a health evaluation survey of active employees found no evidence of hematological or liver effects (Ott et al. 1983a, 1983c). Other epidemiological studies are limited to studies of pregnancy outcome among female laboratory workers exposed to a variety of solvents, including acetone (Axelsson et al. 1984) and among female factory workers exposed to acetone in Russia (Nizyaeva 1982). No statistically significant increased incidence of miscarriage, perinatal death rate, or malformations of offspring was found in the laboratory workers (Axelsson et al. 1984). Miscarriages and neonates with reduced body weights and length were reported for the factory workers (Nizyaeva 1982), but this study was considered unreliable because of reporting limitations. Acute inhalation studies in volunteers (Matsushita et al. 1969a, 1969b; Nelson,et al. 1943) and on-site medical evaluations of workers on a single workday (Raleigh and McGee et al. 1972; Ross 1973) have found that acetone is irritating to the nose, throat, trachea, lungs, and eyes and may cause unconsciousness if exposure levels are high enough (Ross et al. 1973). Acute experimental studies in humans also found hematological effects, which might also indicate immunological effects (Matsushita et al. 1969a, 1969b) and neurobehavioral effects (Dick et al. 1989; Matsushita et al. 1969a, 1969b). Case reports of patients exposed to acetone vapors by inhalation and/or dermally during and after application of hip casts have found cardiovascular effects (increased pulse rates), gastrointestinal effects (vomiting of blood, hemorrhage), and neurological effects (headache, dizziness, listlessness, mystagmus, difficulty speaking, coma, collapse) (Chatterton and Elliot 1946; Fitzpatrick and Claire 1947; Harris and Jackson 1952; Hift and Pate1 1961; Pomerantz 1950; Renshaw and Mitchell 1956; Strong 1984). No indication that the liver and kidney were target organs, based on clinical chemistry parameters, was found in humans exposed under laboratory conditions (DiVincenzo et al. 1973). Information on effects of acute oral exposure of humans was derived from case reports of accidental or intentional ingestion of acetone and indicate that ingestion causes coma (Gamis and Wasserman 1988; Gitelson et al. 1966; Ramu et al. 1978; Sakata et al. 1989), erosions in the buccal cavity, and possible diabetes-like symptoms (Gitelson et al. 1966). Some of these cases were confounded by coexposure to other narcotic chemicals, such as alcohol and liquid cement. Direct application of acetone to the skin of humans resulted in skin irritation and degenerative changes in the epidermis (Lupulescu et al. 1972, 1973; Lupulescu and Birmingham 1975, 1976), and a case of contact dermatitis was reported (Tosti et al. 1988). Populations likely to be exposed to acetone include workers in industries that process and use acetone, such as, paint, plastic, artificial fibers, and shoe factories. Professional painters and commercial cleaners, laboratory workers, and manicurists, if they still use acetone-containing nail polish remover, can also have greater exposure than the general population. Inhalation and dermal exposure are the

most likely routes of exposure for workers. Cigarette smokers, people living near landfill sites that contain acetone, near highways (automobile exhaust), or incinerators will also have greater exposure primarily by inhalation than the general population. Any epidemiological studies designed for these populations should look for neurological, immunological, hematological, hepatic, renal, reproductive, developmental, and genotoxic effects and cancer. This information would be useful for establishing cause/effect relationships and for future monitoring of individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect

Exposure. Acetone has been identified in breast milk of lactating women, but nursing mothers represent only a fraction of the general population (Pellizzari et al. 1982). Acetone concentrations in expired air, blood, and urine have been monitored in a number of studies of humans exposed to acetone in the workplace (Brugnone et al. 1978, 1980; Fujino et al. 1992; Kawai et al. 1990a, 1992; Pezzagno et al. 1986) as well as by inhalation in controlled laboratory situations (Dick et al. 1989; DiVincenzo et al. 1973; Matsushita et al. 1969a, 1969b; Nomiyama and Nomiyama 1969a, 1969b; Pezzagno et al. 1986; Stewart et al. 1975; Wigaeus et al. 1981), and correlations with exposure levels have been found. Acetone levels in expired air, blood, and urine have also been used to determine whether patients admitted to the hospital in comatose conditions had ingested acetone (Ramu et al. 1978; Sakata et al. 1989). Gastric contents can also be analyzed for determining whether acetone was ingested (Fastlich 1976). In addition, the detection of the odor of acetone in the breath can alert a physician that a patient might have been exposed to acetone (Harris and Jackson 1952; Strong 1944). Carbon dioxide is the main end metabolite of acetone, but has not been used to monitor for exposure, probably because much unchanged acetone is expired and monitoring directly for acetone is more specific. However, acetone is cleared from breath, urine, and blood of humans within l-3 days and shows little tendency to accumulate (Brown et al. 1987; Dick et al. 1989; DiVincenzo et al. 1973; Fukabori et al. 1979; Gamis and Wasserman 1988; Matsushita et al. 1969a, 1969b; Sakata et al. 1989; Wigaeus et al. 1981), so these methods are useful for monitoring only for recent occupational exposure or from accidental or intentional ingestion. Carbon dioxide derived from acetone is also cleared rapidly. This implies that monitoring for more remote exposure is not possible. Other metabolites of acetone enter gluconeogenic pathways, so their origin from exogenous acetone would be masked. Furthermore, because acetone is a metabolite of isopropyl alcohol, it would be difficult to distinguish whether a person was exposed to isopropyl alcohol or acetone. Furthermore, endogenous levels of acetone vary widely due to a variety of factors. As discussed in Section 2.9.3, an abstract indicated

that acetone increased the levels of DNA adducts in rats exposed via drinking water (Cunningham and Gold 1992).

Effect. The consistently observed effect of acetone exposure in animals is the induction of microsomal enzymes, particularly cytochrome P-450IIE1, which can be detected by immunochemical methods using antibodies to it (Johansson et al. 1988). The enzyme induction has been associated with increased liver weights and hepatocellular hypertrophy due to the increased protein content (NTP 1991). Cytochrome P-450IIEl is associated with the metabolism of acetone itself, but acetone is not metabolized to toxic intermediates. However the induction of this enzyme is the mechanism by which acetone potentiates the toxicity of many other chemicals (Brady et al. 1989; Freeman and Hayes 1988; Johansson et al. 1988; Kim et al. 1990; Kobusch et al. 1989; Pankow and Hoffmann 1989; Ronis and Ingelman-Sundberg 1989; Song et al. 1989; Tu et al. 1983; Yoo et al. 1990). Cytochrome P-450IIEl can be induced by a variety of other factors, such as ethanol, fasting, and experimental diabetes (Johansson et al. 1986; Puccini et al. 1990); therefore, the induction is not specific to acetone, and the detection of the enzyme would require liver biopsy and would probably be indicative only of recent exposure. However, an *in vivo* probe to detect elevated levels of cytochrome P-450IIEl in human populations is being developed (see Section 2.9.3). Exposure of rats to acetone has resulted in degeneration of apical microvilli in the kidney (Brown and Hewitt 1984) and nephropathy (NTP 1991), but these effects have not been associated with increased levels of blood urea nitrogen. A strong odor of acetone on the breath and nausea, or high levels of acetone in blood or urine in patients can alert physicians to the possibility of more serious sequelae such as gastrointestinal hemorrhage and narcosis (Harris and Jackson 1952; Strong 1944) or to metabolic acidosis (Gitelson et al. 1966). In rats, acetone exposure resulted in anemia as detected by hematological parameters (American Biogenics Corp. 1986; NTP 1991) and increased testis weight, decreased sperm motility, caudal weight and epididymal weight, and increased incidences of abnormal sperm (NTP 1991). These effects were seen after intermediate-duration exposure. Hematological tests and tests for sperm motility and abnormalities could be used to screen humans for possible hematological effects and effects on fertility. Overt signs of skin irritation could alert physicians to possible degenerative changes, which can be detected by microscopic examination of the epidermis (Lupulescu et al. 1972, 1973). Allergic reactions can be detected by patch testing (Tosti et al. 1988). There does not appear to be a need for additional biomarkers.

Absorption, Distribution, Metabolism, and Excretion. A substantial database exists regarding absorption and excretion of acetone by humans and animals after acute inhalation and oral exposure to acetone (Brown et al. 1987; Charbonneau et al. 1986a, 1986b; Dick et al. 1989; DiVincenzo et al. 1973; Egle 1973; Fukabori et al. 1979; Geller et al. 1979b; Haggard et al. 1944; Hallier et al. 1981; Jakubowski and Wieczorek 1988; Kawai et al. 1992; Landahl and Herrmann 1950; Matsushita et al. 1969a, 1969b; Miller and Yang 1984; Morris 1991; Nomiyama and Nomiyama 1974a; NTP 1988; Pezzagno et al. 1986; Plaa et al. 1982; Price and Rittenberg 1950; Ramu et al. 1978; Sakata et al. 1989; Schrikker et al. 1985, 1989; Skutches et al. 1990; Vangala et al. 1991; Widmark 1919; Wigaeus et al. 1981, 1982) and the information is sufficient to assess relative rates and extent of absorption and excretion. Uptake and excretion are directly proportional to dose and duration of exposure but can be influenced by exercise during exposure and fasting. Acetone does not appear to accumulate to any great extent after repeated exposure, so information on absorption and excretion after intermediate- and chronic-duration exposure does not appear to be necessary. An inhalation study in mice examined the distribution of acetone (Wigaeus et al. 1982), which is widespread regardless of route of uptake. The metabolic pathways of acetone are relatively well understood based on animals studies (Casazza et al. 1984; Hallier et al. 1981; Hetenyi and Ferrarotto 1985; Johansson et al. 1986; Koop and Casazza 1985; Kosugi et al. 1986a, 1986b; Mourkides et al. 1959; Price and Rittenberg 1950; Puccini et al. 1990; Rudney 1954; Sakami and LaFaye 1950, 1951; Skutches et al. 1990). There is some indication that at low doses, the pathways, via methylglyoxal and lactate, predominate, but at higher doses that saturate this pathway, metabolism is shunted to the formate-acetate branch of the propanediol pathway (Kosugi et al. 1986a). Although acetone is absorbed dermally, quantitative data are limited to a study in which an unspecified amount of acetone was applied to the skin of volunteers and levels of acetone were measured in blood, alveolar air, and urine (Fukabori et al. 1979). While the dermal absorption was stated to be fairly rapid, the net amount absorbed and rate of absorption were not determined. Furthermore, inhalation of acetone could not be completely prevented. Additional studies in humans or animals, designed to measure the rate and extent of dermal absorption, would help to fill this gap in understanding the toxicokinetics of acetone. Other than this gap in the database, there appears to be little need for additional information on absorption, distribution, metabolism, and excretion.

Comparative Toxicokinetics. Acetone appears to have similar target organs in animal and humans, such as, the hematological system and the central nervous system. Toxicokinetic studies have been conducted in both humans and animals, especially in humans exposed by inhalation. There appear to be very few differences between animal species, and the dog appears to be a good model for

extrapolating absorption results to humans (DiVincenzo et al. 1973). Metabolic pathways have been elucidated primarily in rats, but mice and rabbits have also been studied. Metabolism involves three different pathways of gluconeogenesis (Casazza et al. 1984; Kosugi et al. 1986a, 1986b). The first step in the metabolism of acetone is dependent on cytochrome P-450IIEl (Casazza et al. 1984), which acetone induces, and this induction has been demonstrated in rats (Johansson et al. 1988), mice (Banhegyi et al. 1988), hamsters (Ueng et a. 1991), and rabbits (Ding and Coon 1990). It appears that the metabolic pathways operate in all species. The distribution of acetone has been studied only in mice exposed by inhalation (Wigaeus et al. 1982). Acetone was widely distributed to organs and tissues throughout the body. This is expected to be true for all species by virtue of its high water solubility, facilitating distribution through the water compartment of the body. There appears to be little need for additional comparative toxicokinetic studies.

Methods for Reducing Toxic Effects. Acetone is readily and passively absorbed from the lungs and gastrointestinal tract into the blood stream (Brown et al. 1987; Charbonneau et al. 1986a; Dick et al. 1989; DiVincenzo et al. 1973; Price and Rittenberg 1959; Sakata et al. 1989; Skutches et al. 1990) and widely to distributed throughout the water compartment (Wigaeus et al. 1982). The only known methods for reducing absorption from the gastrointestinal tract are administration of syrup of ipecac (Stutz and Janucz 1988) and gastric lavage (Sakata et al. 1989). Established methods for reducing body burden are administration of a cathartic, such as magnesium sulfate (Stutz and Janucz 1988) and hemodialysis (Rosansky 1982). The mechanism of the narcotic effects of acetone is not known, but as a solvent, acetone may interfere with the composition of the membranes, altering their permeability to ions (Adams and Bayliss 1968). Developing a method to block this interference might prevent acetone induced coma. Since the metabolites are gluconeogenic precursors, they are probably not toxic. Therefore, acetone itself is probably the toxic agent, and enhancing its metabolism may block its toxic action. However, acetone induces its own metabolism by inducing cytochrome P-450IIEl (Johansson et al. 1986; Puccini et al. 1990). Since ethanol also induces this particular form of P-450IIEl (Johansson et al. 1988; Puccini et al. 1990), the metabolism of acetone might be increased by administering ethanol. Ethanol has been shown to decrease the breath levels of acetone (Jones 1988). However, since acetone potentiates the toxicity of other chemicals by inducing cytochrome P-450IIE1, which enhances the metabolism of the chemicals to reactive intermediates (see Section 2.6), further increasing the cytochrome P-450IIEl levels might be counterproductive in cases of exposure to acetone followed by exposure to the other chemicals. Furthermore, acetone potentiates the central nervous system toxicity of ethanol by inhibiting alcohol dehydrogenase, which is responsible for 90%

of ethanol elimination (Cunningham et al. 1989). Development of other means of enhancing acetone's metabolism might solve this dilemma. The established method for mitigating acute acetone poisoning is the administration of a cathartic, and administration of diazepam to alleviate seizures, or phenobarbital if diazepam is ineffective (Stutz and Janucz 1988). No methods were located to mitigate more subtle effects.

2.9.3 On-going Studies

Dr. C.S. Yang of Rutgers University is conducting on-going studies sponsored by the National Institute of Environmental Health Sciences (NIEHS) on the molecular mechanism of the regulation of cytochrome P-450IIEl (CRISP 1993). The specific aims of the project are to examine the role of acetone, other ketone bodies, and hormones in the induction of this enzyme in rat liver; to characterize the molecular events in the regulation of P-45011El by measuring transcriptional and translational activities and the stabilities of mRNA and proteins; to investigate sex-related differences and hormonal regulation of P-450IIEl in the mouse kidney at the physiological, biochemical, and molecular biological levels; and to understand the active site dynamics and catalytic function of P-450IIEl by examining the structural characteristics of its substrates, by deriving structural information from the amino acid sequence, by modifying specific amino acid residues in the active site with a site-directed mutagenesis approach, and by studying the metabolism and toxicity of environmental chemicals.

Dr. K.E. Thummel of the University of Washington is conducting on-going studies sponsored by the National Institute of General Medical Sciences on whether humans exposed to acetone and other inducers of cytochrome P-450IIE1, or with altered metabolic states, will have elevated levels of this enzyme that can be identified by an *in vivo* probe (CRISP 1993). The utility of the probe candidates will be validated by determining the *in vitro* catalytic specificity of the probe toward human liver P-450IIEl; identifying an *in vivo* metabolic clearance parameter that reflects intrinsic P-450IIEl catalytic activity; and determining whether the *in vivo* clearance parameter predicts direct measurement of hepatic P-450IIEl levels in normal and isoniazid-treated populations.

A number of recent abstracts of studies yet to be published were located covering topics related to toxicokinetics and enzyme induction, These studies are described below.

In rats treated intraperitoneally with acetone, the concentration of acetone in expired air was 40% and the half-life was 4 hours (Teramoto et al. 1989).

Fed pregnant rats on gestational day 20 had slightly higher endogenous serum acetone levels compared with nonpregnant controls, and acetone monooxygenase activity was significantly lower in the pregnant rats than in the nonpregnant rats (Casazza et al. 1990). Administration of acetone in the drinking water for 5 days increased the acetone monooxygenase activity, but the activity was lower than in acetone treated nonpregnant rats. Immunoblot analysis showed that cytochrome P-45OIIEl decreased progressively during pregnancy and rapidly returned to normal after parturition. The decrease in P-45011El was accompanied by a gradual decrease in P-450IIEl mRNA. The results indicated that liver P-45011El is suppressed in the pregnant rat, while the levels still respond to acetone induction. A pretranslational mechanism was suggested for P-450IIEl suppression.

Serum levels of endogenous acetone were 26 μmol/mL in 20-day pregnant rats and 14 μmol/mL in the pooled blood from litters of fetal siblings (Casazza et al. 1988). No increase in maternal blood acetone was seen on day postpartum day 1, but the levels in pups were markedly increased. Measurable levels of serum acetol and 1,2-propanediol were also found in the 2- to 3-day-old pups. Injection of acetol into the pups resulted in a nine-fold increase in 1,2-propanediol levels. The results demonstrate the acetone is normally present in newborn rats, and that the pups are able to metabolize acetone to 1,Zpropanediol soon after birth.

Acetone added to the culture system increased the incorporation of methionine into cytochrome P-450IIEl in rabbit hepatocytes, indicating that the acute phase of acetone induction of this enzyme partly involves an increased rate of P-450IIEl protein synthesis (Kraner et al. 1991).

Xenobiotic metabolizing activities associated with cytochrome P-45011El were elevated in liver microsomes from acetone treated rats (Menez et al. 1990). Coadministration of phorbol myristate acetate, an activator of protein kinase c, with acetone suppressed P-450IIEl content and the activities of the associated oxidases, indicating that the induction of P-450IIEl by acetone involves inhibition of protein kinase c.

Acetone inhibited the tumor promoting activity of phorbol myristate acetate following initiation with dimethylbenz[a]anthracene on mouse skin (Weiss et al. 1988).

N-nitrosodimethylamine demethylase activity in rat hepatoma was increased by treating the rats with acetone (Hu et al. 1990).

The levels of hepatic N7-methylguanine and O6-methylguanine DNA adducts were significantly increased by treatment of rats with 10% acetone in drinking water for 10 days (Cunningham and Gold 1992).

3. CHEMICAL AND PHYSICAL INFORMATION

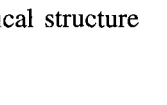
3.1 CHEMICAL IDENTITY

Data pertaining to the chemical identities of acetone, the simplest aliphatic ketone, are listed in Table 3-l.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of acetone are given in Table 3-2. The physical properties of acetone, such as high evaporation rate, low viscosity, and miscibility with water and several organic solvents make it suitable for use as a solvent (Krasavage et al. 1982). Because of its ability to undergo addition, oxidation/reduction, and condensation reactions, acetone is used as a raw material in the chemical synthesis of many commercial products (Nelson and Webb 1978).

TABLE 3-1. Chemical Identity of Acetone

Characteristic	Information	Reference
Chemical name	Acetone	HSDB 1992
Synonym(s)	Dimethyl ketone; 2-propanone; beta-ketopropane	HSDB 1992
Registered trade name(s)	No data	
Chemical formula	C_3H_6O	
Chemical structure		
Identification numbers:		
CAS registry	67-64-1	HSDB 1992
NIOSH RTECS	AL3150000	HSDB 1992
EPA hazardous waste	U002; F003	HSDB 1992
OHM/TADS	7216568	HSDB 1992
DOT/UN/NA/IMCO shipping	UN1090	HSDB 1992
HSDB	41	HSDB 1992
NCI	ND	HSDB 1992

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

TABLE 3-2. Physical and Chemical Properties of Acetone

Property	Information	Reference
Molecular weight	58.08	Riddick et al. 1986
Color	Colorless	HSDB 1992
Physical state	Liquid	HSDB 1992
Melting point	-95.35°C	HSDB 1992
Boiling point	56.2°C at 1 atm	HSDB 1992
Density:		
at 20°C	0.78998 g/mL	Riddick et al. 1986
at 25°C	0.78440 g/mL	Riddick et al. 1986
at 30°C	0.78033 g/mL	Riddick et al. 1986
Odor	Mildly pungent and aromatic	Nelson and Webb 1978
Odor threshold:		
Water	20 ppm (w/v)	Amoore and Hautala 1983
Air (absolute)	13–20 ppm (v/v)	Amoore and Hautala 1983; Hellman and Small 1974
100% odor recognition	100–140 ppm	Hellman and Small 1974; Leonardos et al. 1969
Solubility:		
Water at 20°C	Completely miscible	HSDB 1992
Organic solvent(s)	Soluble in benzene and ethanol	HSDB 1992
Partition coefficients:		
Log K_{ow}	-0.24 (recommended value)	Collander 1951; Sangster 1989
Log K_{oc}	0.73 (estimated)[a]	Lyman 1982
Vapor pressure at 20°C	181.72 mmHg	Riddick et al. 1986
Henry's law constant:		
at 25°C	4.26×10^{-5} atm·m^3/mol	Rathbun and Tai 1987
Autoignition temperature	465°C	HSDB 1992
Flashpoint (closed cup)	-20°C	HSDB 1992
Flammability limits in air at 25°C	Lower, 2.15%; upper, 13.0%	HSDB 1992
Conversion factors:		
in air at 25°C	1 ppm = 2.374 mg/m^3	HSDB 1992
Explosive limits	Lower, 2.6% in air (v/v); upper, 12.8% in air (v/v)	HSDB 1992 HSDB 1992

[a]Estimated by regression equation 4-13 in Lyman (1982)

w/v = weight per volume; v/v = volume per volume

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

In 1991, 12 companies at 14 locations produced acetone in the United States. The U.S. manufacturers of acetone in 1991, their respective manufacturing sites, and production capacities are shown in Table 4-l (SRI 1992).

Exxon Chemical Americas also produced acetone in the United States in 1990 (USITC 1991).
Table 4-2 lists the companies that process acetone and the intended use and maximum amounts of the chemical stored on site.

The reported total production volume of acetone in the United States was 2,330 million pounds in 1990 (USITC 1991). Historically, the reported growth of acetone demand was 2.1% per year during the 1980's and is expected to grow at a rate of 2.5% per year through 1994 (CMR 1990).

Most acetone is manufactured by one of two processes, cumene peroxidation or isopropanol dehydrogenation (SRI 1991). In the peroxidation process, cumene is oxidized to hydroperoxide, which is cleaved to yield acetone and phenol. In the dehydrogenation process, isopropanol is catalytically dehydrogenated to yield acetone and hydrogen (Nelson and Webb 1978). Relatively small quantities of acetone are recovered as a byproduct from the production of hydroquinone and oxidation of propylene oxide (SRI 1991).

4.2 IMPORT/EXPORT

The amount of acetone exported by the United States has increased in recent years. Export volume in 1987 was 5% of total production volume (CMR 1987). By 1990, export volume had increased to an estimated 138 million pounds, or 6% of the 2,330 million pounds produced (CMR 1990). The United States imported 110 million pounds of acetone in 1989, and import volume is expected to increase through 1994, due to a projected increase in domestic demand.

TABLE 4-1. U.S. Manufacturers of Acetone in 1991[a]

Manufacturer	Location	Annual capacity, (million of pounds)
Allied Signal, Inc.	Philadelphia, PA	490
Aristech Chemical Corp.	Haverhill, OH	392
ARCO Chemical Co.	Bayport, TX	62
BTL Speciality Resins Corp.	Blue Island, IL	53
Dow Chemical U.S.A.	Oyster Creek, TX	335
Eastman Chemical Co.	Kingsport, TN	25
General Electric Co.	Mount Vernon, IN	380
Georgia Gulf Corp.	Pasadena, TX Plaquemine, LA	100 2,656
The Goodyear Tire & Rubber Co.	Bayport, TX	12
Shell Oil Co.	Deer Park, TX Wood River, IL	459 350
Texaco, Inc.	El Dorado, KS	55
Union Carbide Corp.	Institute, WV	170
Total		3,148

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

State[b]	Number of facilities	Range of maximum amounts on site in thousands of pounds[c]	Activities and uses[d]
AK	1	0.1-0.9	1, 5
AL	46 (1)[e]	0-9,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
AR	50 (4)[e]	0-999	1, 2, 3, 5, 6, 8, 9, 11, 12, 13
AZ	24 (2)[e]	0-999	1, 3, 5, 8, 11, 12, 13
CA	220 (13)[e]	0-499,999	1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13
CO	17	0-999	8, 11, 12, 13
CT	27 (5)[e]	0.1-9,999	1, 2, 3, 5, 7, 8, 9, 11, 12, 13
DE	12 (1)[e]	0.1-99	2, 3, 7, 9, 10, 11, 12, 13
FL	107 (3)[e]	0-999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
GA	80 (10)[e]	0-999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
HI	1	1-9	13
IA	36 (2)[e]	0.1-999	1, 2, 3, 7, 8, 9, 10, 11, 12, 13
ID	9	1-99	1, 2, 3, 6, 12, 13
IL	110 (7)[e]	0.1-99,999	1, 3, 4, 7, 8, 9, 10, 11, 12, 13
IN	132 (2)[e]	0-49,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13
KS	34 (2)[e]	0.1-9,999	1, 3, 4, 8, 10, 11, 12, 13
KY	41 (3)[e]	0.1-9,999	1, 5, 7, 8, 10, 11, 12, 13
LA	37 (1)[e]	0-499,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13
MA	66 (5)[e]	0-999	2, 3, 8, 9, 10, 11, 12, 13
MD	17 (1)[e]	0.1-99	1, 2, 3, 5, 8, 9, 11, 13
ME	23 (2)[e]	0-999	1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 13
MI	140 (5)[e]	0-49,999	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13
MN	63 (2)[e]	0.1-999	1, 2, 3, 5, 7, 8, 9, 11, 12, 13
MO	71	0.1-99,999	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13
MS	31 (3)[e]	0-999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13
MT	1	1-9	1, 5
NC	154 (5)[e]	0-9,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
ND	2	0.1-99	12, 13
NE	17	0-99	8, 11, 12, 13
NH	16 (1)[e]	0.1-99	1, 2, 3, 6, 8, 9, 11, 12, 13
NJ	98 (4)[e]	0-9,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
NM	8	0.1-99	12, 13
NV	3 (1)[e]	1-99	8, 11, 13
NY	89 (6)[e]	0.1-999	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13
OH	157 (5)[e]	0-99,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
OK	13	0.1-99	2, 3, 8, 10, 11, 12, 13
OR	46 (2)[e]	0-999	1, 5, 6, 7, 8, 9, 10, 11, 12, 13
PA	130 (9)[e]	0-9,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
PR	25	1-9,999	2, 3, 4, 7, 8, 10, 11, 12, 13
RI	18 (1)[e]	1-99	1, 5, 9, 10, 11, 12, 13
SC	55 (1)[e]	0-9,999	1, 2, 3, 4, 5, 8, 9, 11, 12, 13
SD	3	1-9	13

TABLE 4-2 Facilities That Manufacture or Process Acetone[a] *(Continued)*

State[b]	Number of facilities	Range of maximum amounts on site in thousands of pounds[c]	Activities and uses[d]
TN	83 (2)[e]	0-49,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
TX	166 (4)[e]	0-99,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
UT	16	0-99	3, 8, 10, 11, 12, 13
VA	81 (2)[e]	0-9,999	1, 2, 3, 5, 8, 9, 10, 11, 12, 13
VT	4 (1)[e]	1-99	8, 12, 13
WA	65 (5)[e]	0-999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WI	75 (5)[e]	0-99,999	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13
WV	16	0-49,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13

[a]Derived from TRI90 (1992)
[b]Post office state abbreviations
[c]Data in TRI are maximum amounts on site at each facility.
[d]Activities/Uses:

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

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

4.3 USE

Acetone is used primarily as an intermediate in chemical production and as a solvent (Nelson and Webb 1978). In 1989, 40% of the available acetone was used in the production of methyl methacrylate, methacrylic acid, and higher methacrylates; 20% was used as a solvent; 13% was used in the production of bisphenol A; 10% was used in the production of methyl isobutyl ketone and methyl isobutyl carbinol; 6% was used in drug and pharmaceutical applications; 5% accounted for miscellaneous uses; and 6% was exported (CMR 1990).

4.4 DISPOSAL

A small amount of acetone is regenerated from solvent wastes produced during its use by reclaiming processes (Kupferschmid and Perkins 1986). Acetone can be removed from waste water by air stripping (HSDB 1992), but the vapor phase acetone generated during stripping requires a suitable disposal method. The three methods commonly used for the disposal of waste containing acetone are underground injection, burial in sanitary landfill, and incineration. The underground injection of acetone-containing waste is allowed under the amended Section 148.10 of Code of Federal Regulations (EPA 1991b). The land disposal of waste waters containing spent acetone is allowed under Section 268.41 of the Code of Federal Register as long as the concentrations of acetone and other permissible spent cosolvents in the waste do not exceed 0.05 and 0.59 mg/L, respectively (EPA 1988a). Incineration under controlled conditions (to attain complete combustion) is one of the better methods of disposal for acetone, and incineration is easier when acetone is mixed with a more flammable solvent. The suitable methods for the destruction of acetone are fluidized bed incineration at a temperature of 450-980°C and residence times of seconds or rotary kiln incineration at 820-1,600ºC and residence times of seconds (HSDB 1992).

5. POTENTIAL FOR HUMAN EXPOSURE

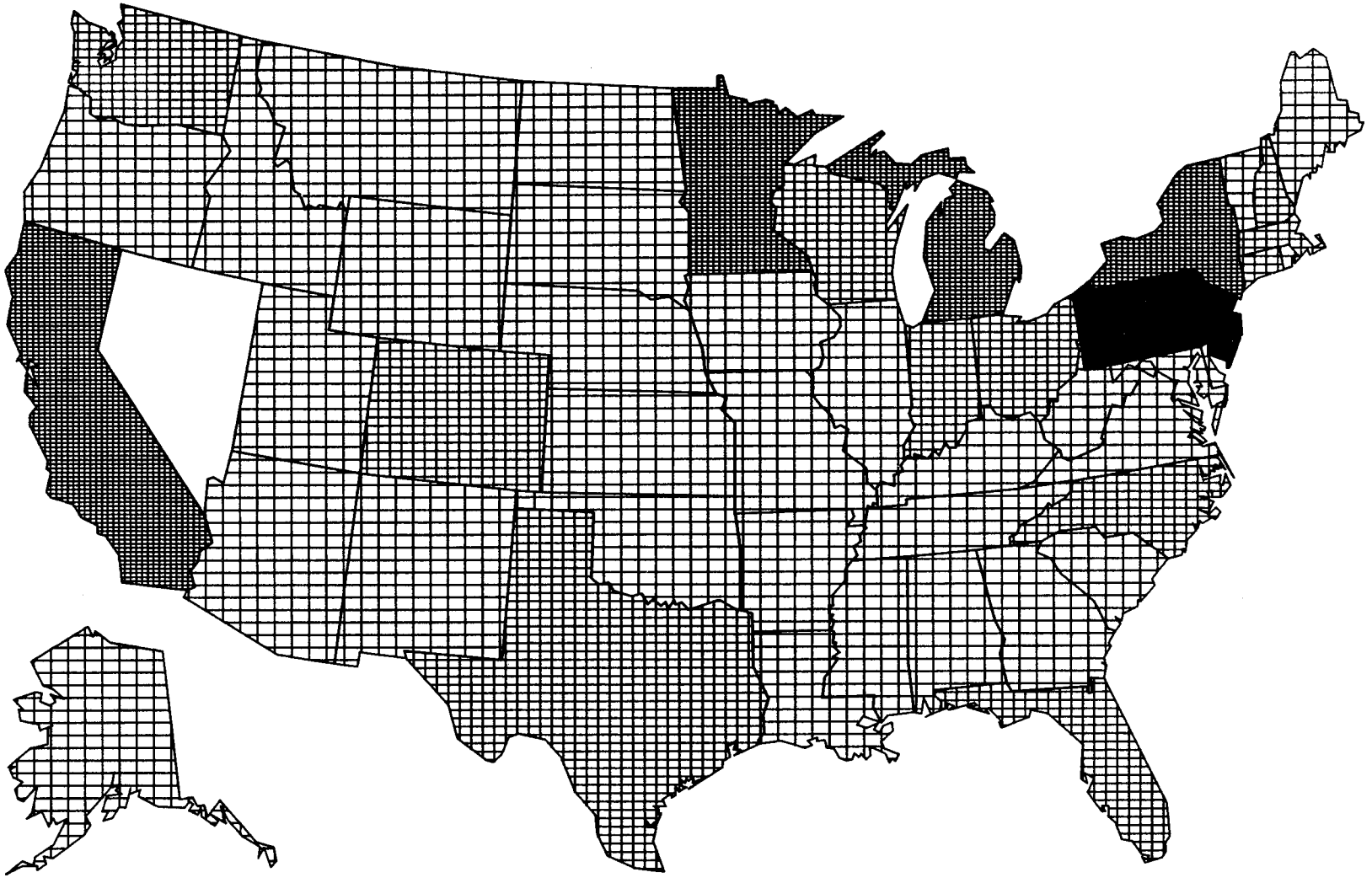
5.1 OVERVIEW

Acetone is emitted into the atmosphere both from natural and anthropogenic (man-made) sources. Natural sources of emission include plants and trees (Graedel et al. 1986; Isidorov et al. 1985; Khalil and Rasmussen 1992), volcanic eruptions (Isidorov et al. 1990), forest fires (Graedel et al. 1986), and insects and microbes (Graedel et al. 1986). Acetone is also produced endogenously and expired in human breath (Conkle et al. 1975). Some important anthropogenic sources of acetone in the air include vehicular exhaust (Graedel et al. 1986), chemical manufacturing (Graedel et al. 1986), tobacco smoke (Manning et al. 1983), wood burning and pulping (Graedel et al. 1986), refuse and polyethylene combustion (Graedel et al. 1986; Hodgkin et al. 1982; NAS 1976), petroleum production (Graedel et al. 1986), certain landfill sites (Hodgson et al. 1992; LaRegina et al. 1986), and solvent use (Graedel et al. 1986). The sensitized photoreaction of dissolved organic matters naturally produces acetone in seawater (Mopper and Stahovec 1986). Chemical manufacturing industries (Abrams et al. 1975), energy-related industries (Mohr and King 1985), and user industries (Abrams et al. 1975) release acetone to surface waters. Acetone is released into groundwater mainly as a result of leaching from municipal and industrial landfills (Brown and Donnelly 1988). The principal sources of acetone in soil are municipal and industrial discharge in landfills (EPA 1988b). Another source is atmospheric deposition (Grosjean and Wright 1983). Acetone is released in soil from natural sources, such as disposed agricultural and food wastes and animal wastes (Graedel et al. 1986).

Acetone has been identified in at least 560 of the 1,350 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HAZDAT 1991). However, the number of sites evaluated for acetone is not known. The frequency of these sites within the United States can be seen in Figure 5-l. Of these sites, 559 are located in the United States and 1 is located in the Commonwealth of Puerto Rico (not shown).

The two processes that are important in determining the fate of acetone in the atmosphere are reaction with hydroxyl radicals and photolysis. The estimated half-life of acetone in the air due to combinations of these two reactions is 22 days (Meyrahn et al. 1986). Because of this reasonably long half-life, acetone is transported long distances from its source of emission. Wet deposition transports

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



*Derived from HAZDAT 1991

atmospheric acetone to surface water and the terrestrial surface (Grosjean and Wright 1983). The most important fate determining process for acetone in water is biodegradation (Rathbun et al. 1982). Because of its high water solubility, acetone does not adsorb significantly to sediment and suspended solids in water. Acetone does not bioconcentrate in aquatic organisms (Rustung et al. 1931), and there is no data on acetone biomagnification in aquatic and terrestrial food chains. Biodegradation is the most important degradative process for acetone in sediment and soil (Rathbun et al. 1982). The important transport processes of acetone in soil are volatilization to the atmosphere and leaching into groundwater.

The levels of acetone in ambient air and water are generally low. The concentration of acetone in the atmosphere in remote areas is ≤1 ppb (volume per volume [v/v]) (1 ppb=0.001 ppm) (Cavanagh et al. 1969; Arnold et al. 1986). Its mean concentration in the atmosphere of rural areas is <3 ppb (Shepson et al. 1991; Snider and Dawson 1985). The mean concentration of acetone in urban air in the United States is 6.9 ppb (Shah and Singh 1988). Acetone concentration in indoor air in the United States is generally slightly higher than outdoor air (8.0 ppb versus 6.9) (Shah and Singh 1988), due to the use of household consumer products containing acetone. The concentration of acetone in open seawater near the Bahamas was 0.35 ppb (Kieber and Mopper 1990). The concentration of acetone in the Potomac River in Virginia was below the detection limit of 40 ppb (Hall et al. 1987), and the level will be higher in water receiving industrial and municipal discharge containing acetone. An industrial landfill leachate in Michigan contained 62 ppm acetone (Brown and Donnelly 1988). An acetone concentration ≤3,000 ppb was detected in a drinking water well in New Jersey (Burmaster 1982). The level of acetone in finished drinking water is generally low (Coleman et al. 1976; Keith et al. 1976), and the reported concentration in drinking water from Seattle, Washington, was 1 ppb (Keith et al. 1976). A concentration of 6 ppb acetone was detected in the sediment of a creek adjacent to a landfill in Louisville, Kentucky (Stonebraker and Smith 1980). Acetone has been detected in the volatile components of several fruits and vegetables (Bartley and Schwade 1989; Lovegren et al. 1979).

The general population is exposed to acetone by inhaling ambient air and by ingesting drinking water and food containing acetone. No data for the total daily intake of acetone for the general population were located. There is a great deal of evidence that workers in certain industries, such as certain paint, plastic, artificial fiber, and shoe factories are exposed to much higher levels of acetone than the general population (Kawai et al. 1990a; Pezzagno et al. 1986). Professional painters, and commercial and household cleaners are also likely to be exposed to higher acetone concentrations than the general

population. Among the general population, smokers, frequent users of nail polish removers and people who live near certain landfill sites (emitting higher than ambient levels of acetone) or other industrial sources of emission are susceptible to higher exposure concentrations of acetone.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Acetone is emitted into the atmosphere both from natural and anthropogenic (man-made) sources. Natural sources of emission include plants and trees. Acetone has been detected in a number of plant volatiles including onions, grapes, cauliflower, tomatoes, wild mustard, beans, and peas (HSDB 1992), and emissions have been detected from a variety of trees including willow, aspen, birch, balsam poplar, oak, fir, pine, juniper, cedar, and cypress (Isidorov et al. 1985; Khalil and Rasmussen 1992). Acetone is produced endogenously and released as a component of human breath (Conkle et al. 1975; Krotoszynski 1977; Trotter et al. 1971). Volatiles from animal wastes, microbes, and insects are also examples of natural sources of acetone in the air (Graedel et al. 1986). In addition, forest fires and volcanic eruptions emit acetone into the atmosphere (Graedel et al. 1986; Isidorov et al. 1990).

Some important anthropogenic sources of acetone in the air are automobile and diesel exhaust (Barber and Lodge 1963; Jonsson et al. 1985; Lloyd 1978), chemical manufacture (Graedel et al. 1986), tobacco smoke (Manning et al. 1983), wood burning and pulping (Graedel et al. 1986; Kleinienst et al, 1986; Lipari et al. 1984), polyethylene burning (Hodgkin et al. 1982), refuse combustion (NAS 1976), petroleum production (Graedel 1978), certain landfill sites (Hodgson et al. 1992; LaRegina et al. 1986; Militana and Mauch 1989), and solvent uses (Medinilla and Espigares 1988). Acetone is also formed in the atmosphere from the photochemical oxidation of propane (Arnold and Ziereis 1986; Singh and Hanst 1981) and possibly from propylene oxide and epichlorohydrin (Spicer et al. 1985). Atmospheric emissions are also likely from several consumer products including nail polish removers, particle board (Tichenor and Mason 1988), carpet backing (Hodgson et al. 1993), some paint removers (Hahn and Werschulz 1986), and a number of liquid/paste waxes or polishes (Knoeppel and Schauenburg 1989; Sack et al. 1992). Certain detergents/cleansers (Knoeppel and Schauenburg 1989; Sack et al. 1992), adhesives, and carburetor and choke cleaners (EPA 1989) are also known to contain acetone.

Acetone released into air from facilities in each state in the United States that manufactured or processed acetone during 1990 are listed in Table 5-l (TR190 1992). According to TR190 (1992), an estimated total of 180 million pounds of acetone, amounting to 96.7% of the total environmental release, was discharged to the air from manufacturing and processing facilities in the United States in 1990. The TRI data should be used with caution since only certain types of facilities were required to report. This is not an exhaustive list. From the monitoring data on levels of acetone in pristine areas and urban/suburban areas (see Section 5.4.1), it seems likely that the total emission of acetone in the atmosphere from anthropogenic sources exceeds the total emission from natural sources.

5.2.2 Water

Acetone is released into surface water as waste water from certain chemical manufacturing industries (Gordon and Gordon 1981; Hites and Lopez-Avila 1980; Jungclaus et al. 1978). It is also released in water from energy-related industries, such as coal-gasification (Mohr and King 1985; Pellizzari et al. 1979) and oil shale processing (Hawthorne and Sievers 1984; Pellizzari et al. 1979). Acetone was found in 27 of 63 effluent waters from a wide range of chemical industries in the United States (Perry et al, 1979). A survey of industrial effluents indicates that acetone was detected in effluents from various industrial products such as, paper, plastic, pharmaceutical, specialty cleaning and polishing products, paint and allied products, gum and wood chemicals, cyclic intermediates, industrial organic chemicals, gypsum products, and paper board products (Abrams et al. 1975).

Acetone is released to groundwater as a result of leaching from municipal and industrial landfills (Brown and Donnelly 1988; Gould et al. 1983; Sawhney and Raabe 1986; Steelman and Ecker 1984; Stonebraker and Smith 1980). Leaching from polyethylene distribution pipes may be a source of acetone in drinking water (Anselme et al. 1985). One of the sources of acetone in seawater is the sensitized photoreaction of dissolved organic matters (Mopper and Stahovec 1986). The releases of acetone to water from facilities that manufactured or processed acetone in states within the United States during 1990 are reported in Table 5-l (TR190 1992). According to TR190 (1992), an estimated total of 1.28 million pounds of acetone, amounting to 0.7% of the total environmental release, was discharged to the water from manufacturing and processing facilities in the United States in 1990. In addition, these facilities discharged an estimated 12.2 million pounds of acetone, amqunting to 6.6% of the total environmental release to municipal waste water of publicly owned treatment works (POTW) in 1990 (TR190 1992).

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

State[c]	Number of facilities	Range of reported amounts released in thousands of pounds[b]						
		Air	Underground injection	Water	Land	Total Environment[d]	POTW[e] transfer	Off-site waste transfer
AK	1	22.5-22.5	0.0-0.0	2.5-2.5	0.0-0.0	25.0-25.0	0.0-0.0	0.0-0.0
AL	46	0.0-240.6	0.0-0.0	0.0-7.8	0.0-16.0	0.0-240.9	0.0-0.3	0.0-30.7
AR	50	0.3-540.0	0.0-0.0	0.0-14.9	0.0-0.3	0.3-540.0	0.0-0.0	0.0-41.3
AZ	24	0.0-1835.1	0.0-0.0	0.0-0.0	0.0-49.6	0.0-1835.1	0.0-43.0	0.0-68.5
CA	220	0.0-160.3	0.0-0.0	0.0-63.0	0.0-0.0	0.0-160.3	0.0-56.5	0.0-132.0
CO	17	0.0-228.1	0.0-0.0	0.0-0.0	0.0-0.0	0.0-228.1	0.0-12.9	0.0-38.2
CT	27	0.0-81.2	0.0-0.0	0.0-400.0	0.0-0.0	0.0-414.6	0.0-378.9	0.0-178.0
DE	12	0.1-71.7	0.0-0.0	0.0-0.0	0.0-0.0	0.1-71.7	0.0-40.5	0.0-41.1
FL	107	0.0-1114.6	0.0-64.0	0.0-6.3	0.0-0.3	0.1-1114.6	0.0-397.3	0.0-198.3
GA	80	0.0-950.0	0.0-0.0	0.0-17.0	0.0-0.8	0.0-952.2	0.0-290.0	0.0-201.5
HI	1	9.7-9.7	0.0-0.0	0.0-0.0	0.0-0.0	9.7-9.7	0.0-0.0	0.0-0.0
IA	36	0.0-490.0	0.0-0.0	0.0-0.3	0.0-0.2	0.0-490.0	0.0-0.8	0.0-14.8
ID	9	1.0-57.0	0.0-0.0	0.0-7.1	0.0-5.7	1.0-57.9	0.0-0.3	0.0-37.2
IL	110	0.0-862.0	0.0-0.0	0.0-6.0	0.0-0.3	0.0-862.0	0.0-302.6	0.0-259.5
IN	132	0.0-2480.0	0.0-0.0	0.0-0.9	0.0-0.3	0.0-2,480.0	0.0-190.0	0.0-2600.0
KS	34	0.0-330.0	0.0-0.0	0.0-7.0	0.0-0.0	0.0-337.0	0.0-92.8	0.0-39.6
KY	41	0.1-760.0	0.0-0.0	0.0-4.7	0.0-0.3	0.1-760.0	0.0-0.3	0.0-191.4
LA	37	0.0-128.0	0.0-1500.0	0.0-17.1	0.0-0.5	0.0-1510.9	0.0-0.0	0.0-70.5
MA	66	0.0-430.6	0.0-0.0	0.0-21.7	0.0-4.3	0.0-430.6	0.0-6.5	0.0-233.7
MD	17	0.0-57.0	0.0-0.0	0.0-0.0	0.0-0.0	0.0-57.0	0.0-30.0	0.0-54.1
ME	23	1.1-165.4	0.0-0.0	0.0-11.0	0.0-4.6	1.3-165.4	0.0-1.3	0.0-20.8
MI	140	0.0-824.0	0.0-775.9	0.0-7.5	0.0-1.5	0.0-1553.3	0.0-748.0	0.0-104.2
MN	63	0.3-175.6	0.0-0.0	0.0-19.0	0.0-0.1	0.3-175.6	0.0-25.4	0.0-62.1
MO	71	0.1-402.2	0.0-0.0	0.0-0.0	0.0-0.3	0.1-402.2	0.0-53.0	0.0-83.0
MS	31	0.0-435.2	0.0-0.0	0.0-13.0	0.0-0.1	0.0-435.2	0.0-0.0	0.0-7.3
MT	1	5.9-5.9	0.0-0.0	6.8-6.8	0.0-0.0	12.7-12.7	0.0-0.0	0.0-0.0
NC	154	0.0-503.4	0.0-0.0	0.0-9.3	0.0-0.3	0.0-503.4	0.0-141.0	0.0-60.0
ND	2	10.1-16.5	0.0-0.0	0.0-0.0	0.0-0.0	10.1-16.5	0.0-0.0	0.0-0.0
NE	17	0.2-68.2	0.0-0.0	0.0-0.0	0.0-0.0	0.2-68.2	0.0-0.0	0.0-15.9
NH	16	0.0-59.2	0.0-0.0	0.0-4.2	0.0-8.5	0.5-59.2	0.0-0.0	0.0-16.2
NJ	98	0.0-931.5	0.0-0.0	0.0-1.2	0.0-48.3	0.0-931.5	0.0-318.4	0.0-570.2
NM	8	1.0-53.0	0.0-0.0	0.0-0.0	0.0-0.3	1.0-53.0	0.0-0.0	0.0-2.4
NV	3	1.3-81.9	0.0-0.0	0.0-0.0	0.0-0.0	1.3-81.9	0.0-0.0	0.0-1.5
NY	89	0.0-2730.0	0.0-0.0	0.0-21.0	0.0-0.8	0.0-2730.3	0.0-340.0	0.0-456.7
OH	157	0.0-1369.0	0.0-630.0	0.0-4.3	0.0-3.7	0.0-1955.0	0.0-75.0	0.0-632.4
OK	13	0.5-165.2	0.0-0.0	0.0-0.0	0.0-0.0	0.5-165.2	0.0-1.7	0.0-46.4
OR	46	0.3-1305.8	0.0-0.0	0.0-7.5	0.0-0.3	0.3-1305.8	0.0-93.7	0.0-115.5
PA	130	0.0-335.1	0.0-0.0	0.0-2.5	0.0-2.5	0.0-335.1	0.0-1894.0	0.0-190.3
PR	25	0.0-1342.4	0.0-0.0	0.0-0.0	0.0-0.1	0.0-1342.4	0.0-201.6	0.0-153.2

TABLE 5-1. Releases to the Environment from Facilities That Manufacture or Process Acetone[a] *(Continued)*

State[c]	Number of facilities	Range of reported amounts released in thousands of pounds[b]						
		Air	Underground injection	Water	Land	Total Environment[d]	POTW[e] transfer	Off-site waste transfer
RI	18	0.0-233.7	0.0-0.0	0.0-6.1	0.0-0.0	0.0-233.7	0.0-0.0	0.0-302.9
SC	55	0.0-2921.8	0.0-0.0	0.0-12.0	0.0-1.6	0.0-2923.8	0.0-1.7	0.0-301.8
SD	3	1.4-32.0	0.0-0.0	0.0-0.0	0.0-0.0	1.4-32.0	0.0-0.0	1.6-6.3
TN	83	0.3-31100.0	0.0-0.0	0.0-42.8	0.0-8.9	0.3-31123.0	0.0-47.2	0.0-85.0
TX	166	0.0-5223.8	0.0-326.0	0.0-9.0	0.0-5.9	0.0-5223.8	0.0-380.0	0.0-462.8
UT	16	0.0-98.2	0.0-0.0	0.0-0.0	0.0-0.0	0.0-98.2	0.0-7.2	0.0-6.6
VA	81	0.0-10530.0	0.0-0.0	0.0-3.8	0.0-5.4	0.0-10535.7	0.0-1889.7	0.0-60.6
VT	4	0.0-41.9	0.0-0.0	0.0-0.0	0.0-0.0	0.0-41.9	0.0-0.0	0.0-10.4
WA	65	0.0-404.2	0.0-0.0	0.0-12.0	0.0-2.7	0.0-404.2	0.0-1.5	0.0-93.1
WI	75	0.0-222.2	0.0-0.0	0.0-2.2	0.0-0.0	0.0-222.2	0.0-42.4	0.0-268.0
WV	16	0.1-3218.1	0.0-0.0	0.0-10.0	0.0-18.7	0.1-3222.4	0.0-483.0	0.0-116.9

[a]Derived form TRI90 (1992)
[b]Data in TRI are maximum amounts released by each facility. Quantities reported here have been rounded to the nearest hundred pounds, except those quantities >1 million pounds, which have been rounded to the nearest thousand pounds.
[c]Post office state abbreviation
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility
[e]POTW = publicly owned treatment works

5.2.3 Soil

Acetone leaches readily in soil (see Section 5.4.3). Therefore, the detection of acetone in leachate and groundwater from municipal and industrial landfills indicates the source of acetone in landfill soils is municipal and industrial discharge. Information regarding the release of acetone from facilities that manufactured or processed the compound in 1990 is reported in Table 5-l (TR190 1992). Table 5-l shows that the amount of acetone released into soil from these facilities accounts for 0.1% of the total environmental release of acetone. Other sources of acetone released into soil include disposal of agricultural and food waste, animal wastes (see Section 5.2.1), and atmospheric wet deposition. Household septic tank effluents are another source of acetone in soil because these effluents containing acetone are discharged into the soil (DeWalle et al. 1985). According to the HAZDAT of ATSDR, acetone was detected in 43% of the soil from Superfund sites tested for acetone (HAZDAT 1991). The information used from the HAZDAT includes data from NPL sites only.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Organic compounds with ambient vapor pressure $>10^{-4}$ mmHg should exist almost entirely in the vapor phase (Eisenreich et al. 1981). Since the vapor pressure of acetone is 181.72 mmHg at 20°C (see Table 3-2), acetone should exist exclusively in the vapor phase in the atmosphere. Furthermore, the collection methods used for the quantification of acetone in the atmosphere (Jarke et al. 1981; Juttner 1986; LaRegina et al. 1986) indicate that atmospheric acetone exists as vapor. Due to the atmospheric half-life, which is on the order of days (see Section 5.3.2.1), acetone will be transported long distances in the air. Although not a large sink (Chatfield et al. 1987), small amounts of acetone will be removed from the atmosphere by wet deposition (Grosjean and Wright 1983), which will transport acetone from the atmosphere to surface water and soil.

The complete miscibility of acetone in water suggests that partitioning of acetone from the water column to sediments and suspended solids in water is not significant. The estimated low value of 0.73 for log K_{oc} (see Table 3-2) also suggests that adsorption of acetone to sediments and suspended solids is not significant. In the absence of water, acetone vapor adsorbs rather strongly to the clay component of soil by hydrogen bonding (Goss 1992; Steinberg and Kreamer 1993). The sorption is

dependent on relative humidity, and increasing the humidity decreases sorption drastically. In water saturated soil or sediment, only organic carbon, as indicated by K_{oc}, and not hydrogen bonding may control the sorption of acetone (Steinberg and Kreamer 1992). The experimental adsorption studies with kaolinite, monkmorillonite, and stream sediments showed very little or no loss of acetone from water to the adsorbents (Rathbun et al. 1982). The transport of acetone from the water column to the atmosphere depends on the Henry's law constant. The Henry's law constant for acetone is $4.26x10^{-5}$ atm-m^3/mol (see Table 3-2). Therefore, volatilization of acetone from water, although not very fast, is significant (Thomas 1982). The volatilization rate of a chemical depends on the characteristics of the chemical and the water and on other ambient conditions (e.g., water depth, suspended solid concentration, water current, wind speed, temperature). Based on an estimation method (Thomas 1982) and a Henry's law constant value of $4.26x10^{-5}$ atm-m^3/mol, the volatilization half-life of acetone from a model river 1 m deep, flowing at a current of 1 m/second with a wind velocity of 3 m/second is about 18 hours. The mean volatilization coefficient for acetone in a model outdoor stream was in the range of $7.15x10^{-4}$ to $14.8x10^{-4}$/minute (Rathbun et al. 1989, 1991). Therefore, the volatilization half-life of acetone from the model stream is in the range of 7.8-16.2 hours. It was concluded that volatilization will control the fate of acetone in water (Rathbun et al. 1989, 1991). Results of a laboratory study (Rathbun et al. 1982) also concluded that volatilization. is one of the important fate determining processes for acetone in streams.

The log K_{ow} value of -0.24 (see Table 3-2) suggests that bioconcentration of acetone in aquatic organisms is not significant. The measured bioconcentration factor for acetone in adult haddock exposed to acetone under static conditions at 7-9°C was <l (Rustung et al. 1931). No data regarding the biomagnification potential of acetone in aquatic organisms were located; however, the low K_{ow} value suggests that biomagnification of acetone from animals of lower to higher trophic level is unlikely.

The two significant transport properties for acetone in soil are volatilization and leaching. Leaching transports acetone from soil to groundwater. The rate of leaching from soil by rainwater depends on the sorption characteristics of acetone in soil. Since acetone may be controlled by K_{oc} in water-saturated soil and has a low K_{oc} value, sorption of acetone in such soil will be weak. The low retention ability will permit acetone to leach into groundwater. A sorption study with moist clay soils indicates that aqueous acetone causes swelling in these soils (Green et al. 1983), and this process may allow the retention of a small fraction of acetone. Groundwater monitoring studies (see Section 5.4.2)

at landfill sites provided evidence of the importance of acetone leaching from soil. Volatilization transports acetone from soil to the atmosphere. The volatility rate of acetone from soil depends on the soil characteristics (moisture content, soil porosity, etc.). Since the acetone is weakly sorbed to soil, the volatility depends primarily on the moisture content of the soil. In dry soil, the volatilization rate from soil surfaces is high due to the high vapor pressure of acetone. In moist soil, the rate of volatilization is similar to acetone in water and depends on the Henry's law constant. Acetone volatilizes moderately under these conditions. The detection of acetone at higher concentrations in downwind air of a landfill site, compared to upwind air (Militana and Mauch 1989), indicates the importance of volatilization as a transport process in soil.

No data regarding the transport of acetone from soil to plants were located.

5.3.2 Transformation and Degradation

5.3.2.1 Air

The reactions of acetone vapor with nitrogen oxides, hydroxyl radicals (OH), singlet molecular oxygen ($^1\Delta_g$, singlet atomic oxygen (O[^{3}P]), and nitrate radicals have been studied. Given the second order rate constants for the reactions of acetone with $^1\Delta_g$ (Datta and Rao 1979) and O(^{3}P) (Lee and Timmons 1977), and the concentrations of singlet molecular and atomic oxygen in the atmosphere (Graedel 1978), these reactions are insignificant in determining the fate of acetone in the atmosphere. The reaction of acetone with nitrate radicals in the atmosphere was also determined to be insignificant (Boyd et al. 1991). Smog chamber studies with acetone and nitrogen oxides conclude that acetone has low reactivity in terms of ozone and nitrogen dioxide formation and that the rate of disappearance of acetone by this process is low (Altshuller and Cohen 1963; Dimitriades and Joshi 1977; Yanagihara et al. 1977). The photochemical oxidation of acetone in the presence of nitrogen oxides produces small amounts of peroxyacetic acid and peroxyacetyl nitrate (Hanst and Gay 1983).

The two significant processes in determining the fate of acetone in the atmosphere are reaction with hydroxyl radicals and photolysis. The rate constant for the reaction of hydroxyl radicals with acetone at 25°C is in the range of 2.2-5.0x10^{-13} cm^3/molecule-second (Cox et al. 1980; Cox et al. 1981; Meyrahn et al. 1986). The estimated average lifetime of acetone due to reaction with hydroxyl radicals is 44.5 days (Meyrahn et al. 1986). The probable pathways for the reaction of acetone with

hydroxyl radicals in the troposphere have been postulated, and methylglyoxal is the primary product of this reaction (Altshuller 1991). Acetone underwent significant photolysis with an artificial light (cutoff wavelength of 270 nm) with a maximum emission intensity of 300 nm (Fujiki et al. 1978). Besides free radicals, the primary products of acetone photolysis in sunlight are carbon dioxide and acetylperoxynitrate (Altshuller 1991). The lifetimes of acetone due to photolysis under cloudless conditions at 40º N latitude, and at sea level during winter and summer are estimated to be 83 and 19 days, respectively (Martinez et al. 1992). Other investigators have estimated that the average atmospheric lifetime of acetone due to photolysis at 40º N latitude is 115.7 days/year (Meyrahn et al. 1986). The estimated average lifetime of acetone at 40º N due to combined hydroxyl radical reaction and photolysis is 32 days/year (Meyrahn et al. 1986), corresponding to a half-life of 22 days. Due to the pressure dependence of the quantum yield, the rate of photodissociation will increase as altitude increases, whereas the reaction rate with hydroxyl radicals will decrease because temperature decreases at higher altitudes. Therefore, the lifetime of acetone in the atmosphere will remain approximately constant with respect to altitude. However, the rate will show a pronounced dependence on latitude with greater losses of acetone occurring near the equator, compared to the poles (Meyrahn et al. 1986).

5.3.2.2 Water

Based on the rate constant for the reaction of acetone with hydroxyl radicals in water at pH 7 ($5.8\text{-}7.7 \times 10^{7}$/M-second) (Anbar and Neta 1967) and the concentration of hydroxyl radicals in eutrophic waters (3×10^{-17}M) (Mill and Mabey 1985), this reaction will not be significant in water. When distilled water or natural water containing acetone were exposed to sunlight for 2-3 days, no photodecomposition of acetone was observed (Rathbun et al. 1982). Therefore, photolysis of acetone in water is not an important process.

Many aerobic biodegradation screening studies with mixed microorganisms from waste-treatment plant effluents, activated sludge, or sewage have examined the biodegradability of acetone (Babeu and Vaishnav 1987; Bhattacharya et al. 1990; Bridie et al. 1979; Ettinger 1956; Gaudy et al. 1963; Hatfield 1957; Heukelekian and Rand 1955; Lamb and Jenkins 1952; Price et al. 1974; Stafford and Northup 1955; Thorn and Agg 1975; Urano and Kato 1986a, 1986b). These studies indicate that acetone is easily biodegradable with acclimatized microorganisms or after a suitable lag period (≈ l day) (Urano and Kato 1986a, 1986b), as long as the initial concentration of acetone is not at a toxic level. For example, acetone at a concentration of 500 mg/L was toxic to microorganisms when biooxidation of

acetone by activated sludge was attempted (Gerhold and Malaney 1966). Biodegradation of acetone was much slower in seawater than in fresh water (Takemoto et al. 1981). After a suitable lag period (5 days), acetone biodegraded quantitatively under anaerobic conditions with anaerobic acetate enriched culture medium (Chou et al. 1979). A biodegradation study of acetone in natural water collected from Lago Lake near Athens, Georgia, determined that the biodegradation kinetics is multiphasic in nature and depends on the substrate concentration. The determined rate of degradation was faster at higher initial concentrations (the maximum concentration used was 0.5 mg/L) (Hwang et al. 1989).

In a laboratory experiment with natural stream water and sediment, no acetone was lost in 338 hours under sterile conditions in closed flasks. However, with nonsterile natural sediment, 100% of the acetone was lost in 500 hours following a lag period of 90 hours. (Rathbun et al. 1982). The authors of this study concluded that biodegradation was one of the important processes for the loss of acetone in streams. Significant loss of acetone due to biodegradation was not observed in a later study where acetone was injected continuously in an outdoor model stream (Rathbun et al. 1988, 1989, 1991, 1993). Attempts to induce biodegradation by adding glucose and a nutrient solution containing bacteria acclimated to acetone were unsuccessful. The authors concluded that the residence time of acetone in the model stream (6 hours) was too short for the bacteria to become acclimated in the water before initiation of biodegradation. However, this explanation may not be valid if attached bacteria, rather than free-floating bacteria, dominate the biodegradation process. As an alternative explanation, the authors indicated that the observed limitation in the nitrate concentration in the stream may be responsible for the lack of acetone biodegradation.

5.3.2.3 Sediment and Soil

The biodegradation studies discussed in Section 5.3.2.2 indicate that biodegradation of acetone in sediment and soil will be significant. However, laboratory or field data examining the biodegradability of acetone in soil are lacking. No evidence was located to suggest that any degradation process other than biodegradation is important in sediment and soil.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Acetone is a volatile compound and is stable in air. Therefore, some monitoring data for the levels of acetone in air are available. The levels of acetone in urban, rural, and remote areas in the United States and the level in the troposphere are shown in Table 5-2.

It is obvious from Table 5-2 that the concentration of acetone in the air around urban areas will be higher than rural and remote areas because of higher emission rates from a larger number of sources. Besides these data, air monitoring data from an urban area (Tulsa, Oklahoma), a rural area (Rio Blanco County, Colorado), and a remote area (Smoky Mountain, Tennessee) are also available (Arnts and Meeks 1981). These data are not presented in Table 5-2 because the samples were collected in Tedlar bags that are known to contaminate air samples with acetone. As a result, the reported acetone concentrations were consistently higher than the values given in Table 5-2. Table 5-2 also indicates that the indoor concentration of acetone is generally higher than the outdoor concentration. Other investigators reported similar results (Jarke et al. 1981). The reason for the higher indoor air concentration is the use of acetone-containing consumer products inside homes. The potential for intrusion of acetone present as soil gas into a house adjacent to a landfill by diffusive and advective routes was found to be low (Hodgson et al. 1992). However, only a single house was studied, and the ambient air in the basement of the house was estimated on two separate occasions and found to be 12 and 82 ppb (v/v).

5.4.2 Water

In a National Organics Reconnaissance Survey (NORS) by EPA involving drinking water supplies from 10 cities in the United States, acetone was qualitatively detected in all 10 water samples. The 10 cities in this survey were Cincinnati, Ohio, Miami, Florida, Ottumwa, Indiana, Philadelphia, Pennsylvania, Seattle, Washington, Grand Forks, North Dakota, Lawrence, Kansas, New York, New York, Terrebonne Parrish, Louisiana, and Tucson, Arizona (Bedding et al. 1982; Coleman et al. 1976; Keith et al. 1976). The determined concentration of acetone in one of the drinking water samples (Seattle, Washington) was 1 ppb (Keith et al. 1976). Acetone has also been detected in water from several artesian wells adjacent to a landfill in Wilmington, Delaware and at a concentration of 0.3 ppb

TABLE 5-2. Acetone Levels in the Troposphere and Urban, Rural, and Remote Areas in the United States and Canada

Location	Monitoring year	Concentration ppb (v/v)	Reference
Tucson, AZ	1982	12.0	Snider and Dawson 1985
Houston, TX	1987–1988	6.1	Lagrone 1991
U.S. outdoor	1980–1986	6.9	Shah and Singh 1988
U.S. indoor	1980–1986	8.0	Shah and Singh 1988
Indoor air of a newly constructed office building, Portland, OR	1987–1988	12.1–28.1	Hodgson et al. 1991
Rural, AZ	1982	2.8	Snider and Dawson 1985
Rural, Ontario	1988	1.7	Shepson et al. 1991
Background, clean air	1988	0.38	Zhou and Mopper 1993
Point Barrow, AK	1967	1.1	Cavanagh et al. 1969
Troposphere (lower)	—	0.7	Dilling 1982
Troposphere (lower)	1984–1985	0.47	Arnold et al. 1986
Troposphere (upper)	1984–1985	0.12	Arnold et al. 1986

in finished drinking water from one of the wells (DeWalle and Chian 1981). The concentration of acetone was ≤3,000 ppb in a drinking water well in New Jersey (Burmaster 1982; Steelman and Ecker 1984).

The concentration of acetone in open ocean water (Tongue of the Ocean, Bahamas) was 6 nM (0.35 ppb) (Kieber and Mopper 1990) whereas the reported mean concentrations in seawater from Straits of Florida and the Eastern Mediterranean were 20 and 30 ppb, respectively (Corwin 1969). The concentration of acetone in the Potomac River, VA was below the detection limit of 40 ppb (Hall et al. 1987). Acetone has been detected in the effluent from a textile plant (Gordon and Gordon 1981) and in effluent water from a specialty chemicals manufacturing plant at a concentration of 200-230 ppm (Jungclaus et al. 1978). The compound has also been detected in groundwater, leachate, and run-off waters from landfill sites (Brown and Donnelly 1988; DeWalle and Chian 1981; Gould et al. 1983; Sawhney and Raabe 1986; Stonebraker and Smith 1980). The concentration of acetone in an industrial landfill leachate in Michigan was in the range of 0.05 to 62.0 ppm (Brown and Donnelly 1988). However, the quality of the reported data is uncertain. Acetone was detected at a mean concentration of 56 ppb in a landfill leachate in Orange County, Florida (Hallbourg et al. 1992).

5.4.3 Sediment and Soil

There are few data regarding the level of acetone in soil and sediment. Acetone has been detected in 43% of the soil samples in Superfund sites for which acetone determination has been made so far. The maximum concentration of acetone in soils from Vega Alta Public Supply well sites in Puerto Rico was 9,500 ppb (ATSDR 1988). The mean concentration of acetone in soil from Summit National Site, Ohio, was 9,484 ppb (dry weight) (EPA 1988b). Acetone has been qualitatively detected in river sediment that received effluents from a specialty chemicals manufacturing plant (Hites and Lopez-Avila 1980). A concentration of 6 ppb μg/kg) acetone was detected in the sediment of a creek adjacent to a landfill in Louisville, Kentucky (Stonebraker and Smith 1980). Because of its high water solubility and low sediment adsorption coefficient, most acetone in an aquatic system will be found in water, rather than in sediment.

5.4.4 Other Environmental Media

Acetone has been qualitatively detected as a volatile component of a number of foods including blue cheese (Day and Anderson 1965), baked potatoes (Coleman et al. 1981), roasted filbert nuts (Kinlin et al. 1972), meat (Grey and Shrimpton 1967; Shahidi et al. 1986), and nectarines (Takeoka et al. 1988). In a study carried out in Czechoslovakia, the concentrations of acetone in samples of milk and cream culture were 79.5 and 0.11 mg/l00 kg, respectively (Palo and Ilkova 1970). Acetone also has been qualitatively detected in breast milk of working mothers, although the study did not identify whether the concentrations of acetone were higher than normal physiologic levels (Giroux et al. 1992). Acetone has been qualitatively detected in 8 of 12 mothers' milk samples collected from two locations in New Jersey, Bridgeville, Pennsylvania, and Baton Rouge, Louisiana (Pellizzari et al. 1982). In kiwi fruit, the acetone concentration comprised 0.2% of total volatile components (Bartley and Schwade 1989). The concentrations of acetone in dry legumes, such as beans (mean of several varieties), split peas, and lentils were 880, 530, and 230 ppb, respectively (Lovegren et al. 1979). The level of acetone in headspace volatiles of Bisbee Delicious apples ranged from 111 to 912 pL/kg-hour (Mattheis et al. 1991). The percent of acetone (of the total) in commercial concentrated aqueous orange essences ranged from 0.003 to 0.009 (Moshonas and Shaw 1990).

Acetone has been detected in occasional rain samples collected in Hanover, Germany (Levsen et al. 1990). The authors were not sure whether the detection of acetone in the rain water was due to contamination of samples during analysis. The concentration of combined acetone and acrolein was 0.05 ppm in a rain water sample from Los Angeles, California (Grosjean and Wright 1983). The investigators could not separate acetone from acrolein by the method used for the determination of carbonyl compounds.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Acetone is endogenously produced by all humans. The general population is exposed to acetone by inhaling ambient air, ingesting food, and drinking water containing acetone. Dermal exposure to acetone may result from skin contact with certain consumer products (e.g., certain nail polish removers, paint removers, and household cleaning and waxing products) (see Section 5.2.1). However, no quantitative data for dermal exposure to acetone from consumer products were located. Assuming concentrations of acetone are 8.0 ppb (18.99 μg/m^3) in indoor air and 6.9 ppb (16.38 ug/m^3) in outdoor

air (Shah and Singh 1988) and that a person inhales 15 m^3/day of indoor air and 5 m^3/day of outdoor air, the estimated inhalation rate of acetone is 0.37 mg/day. No experimental or estimated data were located regarding the daily intake of acetone in the general population in the United States from ingestion of drinking water and food. However, if the concentration of acetone in drinking water is $\leq$1 ppb (see Section 5.4.2), the daily intake for acetone (assuming a person consumes 2 L of drinking water/day) from this source would be negligible.

The acetone concentrations in body fluids and expired air of healthy and diabetic patients are given in Table 5-3. The concentration of acetone in whole blood does not differ from that in plasma (Gavin0 et al. 1986). Even in healthy subjects, the level of acetone in blood/plasma varies with fasting or nonfasting conditions and depends on the weight of the subject. Generally, the blood/plasma acetone concentrations are higher in fasted than nonfasted subjects and higher in subjects who are not obese, compared to obese subjects (Haff and Reichard 1977).

Workers in industries that manufacture and use acetone can be exposed to much higher concentrations of acetone than the general population. For example, the concentrations of acetone in the breathing zone air in a paint factory, a plastics factory, and an artificial fiber factory in Italy were >3.48 mg/m^3 (Pezzagno et al. 1986). The concentration of acetone in the breathing zone air of a fiber-reinforced plastic plant in Japan, where bathtubs were produced, was $\leq$108 mg/m^3 (Kawai et al. 1990a). The inhalation exposure for workers to acetone in a shoe factory in Finland ranged from 25.4 to 393.4 mg/m^3 (Ahonen and Schimberg 1988). Concentrations of acetone in the breathing zone air in shoe factories in Italy were also high (Brugnone et al. 1978). The concentration of acetone in the breathing zone air of a solvent recycling plant in the United States ranged from not detected to 43 mg/m^3 (Kupferachmid and Perkin 1986). High levels of acetone were detected in the occupational air in other industries including chemical, plastic button, and paint manufacturing industries in Italy (Ghittori et al. 1987). Isopropyl alcohol is known to oxidize in the liver and is converted to acetone (Kawai et al. 1990b). Therefore, occupational exposure (printing plants) or accidental ingestion of isopropyl alcohol also produce acetone in expired air, blood, and urine. The National Occupational Exposure Survey (NOES) statistically estimated that 1.51 million workers were potentially exposed to acetone in the United States in 1980 (NIOSH 1989). The NOES database does not contain data on the frequency, duration, concentration, or route of exposure of workers to chemicals.

TABLE 5-3. Concentrations of Acetone in Body Fluids and Expired Air of Humans

Subject	Medium	Concentration	Reference
Healthy (nonfasted)	Blood	0.016 mM (0.93 mg/L)	Gavino et al. 1986
Healthy (fasted)	Plasma	0.8 mM (46.5 mg/L)	Haff and Reichard 1977
Healthy (nonfasted)	Plasma	0.03 mM (1.74 mg/L)	Trotter et al. 1971
Ketoacidotic	Plasma	7.3 mM (424 mg/L)	Trotter et al. 1971
Ketoacidotic	Plasma	5.0 mM (290 mg/L)	Haff and Reichard 1977
Healthy	Urine	4–7 µM (0.23–0.41 mg/L)	Kobayashi et al. 1983
Healthy (endogeneous)	Urine	13.1 µM (0.76 mg/L)	Pezzagno et al. 1986
Diabetic	Urine	11–155 µM (0.64–9.0 mg/L)	Kobayashi et al. 1983
Healthy	Expired air	0.52 ppm (1.23 µg/L)	Jansson and Larsson 1969
Healthy	Expired air	0.02 µM (1.16 µg/L)	Trotter et al. 1971
Healthy	Expired air	0.023 µM (1.3 µg/L)	Phillips and Greenberg 1987
Healthy	Expired air	101.3 ng/L[a] (0.1 µg/L)	Krotoszynski et al. 1979

[a]The reason for the lower value reported by these investigators is not known with certainty but may be due to different sampling procedures (e.g., Teflon® versus polyester sampling bags).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in industries that manufacture or use acetone are one segment of the population at an especially high risk of acetone exposure compared to the general population (see Section 5.5). Professional painters and commercial and household cleaners (certain detergents, cleansers, waxes, or polishes contain acetone) are also likely to be exposed to acetone at higher concentrations than the general population, although experimental data regarding the extent of exposures for this segment of workers were not located. Among the general population, high exposure to acetone may occur among several subgroups. Cigarette smoke contains $\leq$0.54 mg acetone/cigarette (Manning et al. 1983); therefore, smokers are exposed to higher concentrations of acetone than nonsmokers. The content of acetone in certain nail polish removers is high; therefore, individuals who frequently use nail polish removers are exposed to higher levels of acetone than the general population. People who live near landfill sites that emit acetone or those who live near industrial sources of emission (e.g., refinery, incinerator, close to high vehicular traffic areas) are also susceptible to higher exposure concentrations of acetone than the general population that does not reside near these sites. People who consume contaminated well water (see Section 5.4.2) as drinking water are subject to high exposures. People who consume food containing acetone excessively would also be subject to high exposure, especially if associated with other risks.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of acetone is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of acetone.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. Information regarding the physical and chemical properties of acetone necessary to predict its environmental fate and transport processes in the environment is available (see Table 3-2). However, experimental determination of a value for the soil sorption coefficient of acetone from water would be helpful in assessing the potential for leaching and volatility of acetone in different soils.

Production, Import/Export, Use, Release, and Disposal. Data regarding the past and present production volume for acetone and the projected future trend (increase/decrease) in the production volume are known (CMR 1990). In 1990, the reported total production volume of acetone in the United States was 2,330 million pounds (USITC 1991). Recent export and import data for acetone would be helpful. The use pattern of acetone is known. Acetone is present in several household consumer products, but by far a larger amount of acetone is used in industry. Acetone is naturally present in many fruits and vegetables, and there is no information available to indicate that acetone is present in food as a contaminant, due to food processing or packaging. Air is the most likely environmental medium in which significant quantities of acetone contamination will occur during its production and use (TRI90 1992). More data on the rate of acetone release from household consumer products would be useful. The regulations governing the disposal of acetone are well defined. However, more information about the proportion of discarded acetone recovered from recycling, and the proportion lost due to evaporation, ground burial, and incineration would be useful in determining the relative importance of the different routes of exposure.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1988, became available in May of 1990. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The environmental fate of acetone, for the most part, has been well studied (see Section 5.3). Acetone will undergo transport from one environmental medium to another (Grosjean and Wright 1983; Rathbun et al. 1982). Due to its reasonably long half-life in air (22 days) (Meyrahn et al. 1986) and restricted volatilization from groundwater, the atmosphere and groundwater

may act as sinks for acetone. More experimental data regarding the rate of sorption and biodegradation of acetone in soil and its biodegradability in groundwater would be useful to assess the relative importance of the different fate processes.

Bioavailability from Environmental Media. Acetone is readily absorbed in the lung and gastrointestinal tract following inhalation and ingestion. Acetone can also be absorbed from the skin (see Section 2.3). The low value for K_{oc} (see Table 3-2) and a moderate value for Henry's law constant (Rathbun and Tai 1987) suggest that bioavailability of acetone from contaminated water and soil as a result of skin contact may be significant. However, quantitative data regarding the rate and extent of dermal absorption of acetone from contaminated water and soil are lacking. The high water solubility and low K_{oc} value for acetone suggest that bioavailability from ingested soil (e.g., children playing at or near contaminated sites) will be high, but quantitative absorption data are lacking. Data on bioavailability of acetone from ingested plant food were not located but would be helpful.

Food Chain Bioaccumulation. Acetone does not bioaccumulate in aquatic organisms. There is no indication of biomagnification of acetone along the aquatic food chain. Studies indicating the potential for acetone transfer from soil and plants and biomagnification in terrestrial food chains would be useful to confirm its potential for food chain bioaccumulation.

Exposure Levels in Environmental Media. Data regarding the level of acetone in ambient air are available (Lagrone 1991; Shah and Singh 1988; Snider and Dawson 1985). There is a paucity of data regarding the level of acetone in drinking water (Bedding et al. 1982; Coleman et al. 1976; Keith et al. 1976). More comprehensive data on the levels of acetone in the air and water consumed by people who live near acetone-containing hazardous waste sites would be useful in estimating the daily intake from these sources. Although the levels of acetone in the volatile components of several fruits and vegetables are available (see Section 5.4.4), development of data regarding the level of acetone in the total diet would be useful. There are few data regarding the level of acetone in background soil samples.

Reliable monitoring data for the levels of acetone in contaminated media at hazardous waste sites are needed so that the information obtained on levels of acetone in the environment can be used in combination with the known body burden of acetone to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. The levels of acetone in blood/plasma and urine of healthy people, occupationally exposed groups, and diabetic patients are available (see Table 5-3 and Section 5.5). However, data on the levels of acetone in body fluids or tissues of general populations living near sites with higher (than normal) exposure potential (e.g., hazardous waste sites) were not located. This information is useful for assessing the need to conduct health studies on these populations.

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

5.7.2 On-going Studies

No on-going study that would fill the data gaps regarding the transport and fate of acetone in the environment or that evaluates its exposure potential in general population groups susceptible to higher levels of exposure was located.

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

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring acetone, its metabolites, and other biomarkers of exposure and effect to acetone. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Some of the more recent methods for determining the presence of acetone in different biological media are reported in Table 6-1. Prior to the 1960s acetone was considered to be present in only insignificant amounts in hyperketonic states in healthy people. Therefore, the concentration of acetone in biological fluids was rarely measured. The effort to develop analytical methods for the determination of acetone in body fluids increased when it was found that the level of acetone in diabetic patients with severe hyperketonaemia may indeed be significant (Trotter et al. 1971). The parent acetone or its reduction/derivatization product is almost exclusively determined by GC/FID method, although derivatized products can be determined by high-performance liquid chromatography with ultraviolet or fluorescence detectors (Brega et al. 1991; Vairavamurthy et al. 1992). Since the reference acetone values for healthy unexposed people are 0.034-0.120 mmol/L, with a mean of 0.075 mmol/L in plasma, and 0.034-0.095 mmol/L, with a mean value of 0.052 mmol/L in urine (Brega et al. 1991), the available methods have adequate sensitivity to determine the levels of acetone in biological samples of both healthy and diabetic people (Gavin0 et al. 1986; Kobayashi et al. 1983; Phillips and Greenberg 1987; Trotter et al. 1971). The determination of acetone in blood is difficult because acetone is generated as a metabolite from acetoacetate (major metabolite is βhydroxybutyrate), and the quantity produced depends on storage time even when the blood samples are stored at 4°C (Trotter et al. 1971). In addition, acetylacetone present in the plasma is thermally degraded to

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Whole blood	Sample centrifuged to obtain plasma; plasma deproteinized with $HClO_4$	GC-FID	6.6 ng/mL (0.023 nmol)	No data	Preinado et al. 1987
Whole blood	Deproteinized with $HClO_4$ and subjected to purge-and-trap	GC-FID	23.2 ng/mL (0.4 µM)	90–92%	Mangani and Ninfali 1988
Whole blood	Purge-and-trap	GC-MS	0.2 µg/mL	87–107%	Ashley et al. 1992
Serum	Deproteinized with sodium tungstate and cupric sulfate	HRGC-FID	<58 µg/mL (<1 mmol/L)	No data	Smith 1984
Plasma	Acetylacetone in sample enzymatically converted to ß-hydroxybutyrate and sample distilled with H_2SO_4	Automated coulometric with salicylaldehyde in KOH	1.16 µg/mL (0.02 µmol/mL)	95%	Haff and Reichard 1977
Serum	Sample centrifuged and clear filtrate injected into GC	GC-FID	5.8 ng/mL (0.1 nmol/mL)	No data	Cheung and Lin 1987
Urine	Diluted sample derivatized with pentafluorobenzyloxylammonium chloride and extracted with hexane	GC-FID	0.2 µg/mL (3.45 µmol/mL	No data	Kobayashi et al. 1983
Liver	Liver perfusion medium reduced with $NaBH_4$ and an aliquot of reduced solution injected into GC	GC-FID	3.78 µg/mL in perfusate (65 µM)	No data	Holm and Lundgren 1984

TABLE 6-1. Analytical Methods for Determining Acetone in Biological Materials (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Liver, kidney, lung, and adipose tissue	Purge-and-trap	GC-FID	No data	52% (lung) 98% (other tissue)	Holm and Lundgren 1984
Breath	Direct injection into GC	GC-FID	No data	98%	Trotter et al. 1971; Jansson and Larsson 1969

H_2SO_4 = sulfuric acid; FID = flame ionization data; GC = gas chromatography; $HClO_4$ = perchloric acid; HRGC = high resolution gas chromatography; KOH = Potassium hydroxide; MS = mass spectrometry; $NaBH_4$ = sodium borohydride

acetone inside the injection port and on the column, if a gas chromatographic method is used for quantification (Gavino et al. 1986; Trotter et al. 1971).

Two methods that have been used to eliminate the interference from acetylacetone are enzymatic conversion of acetoacetate to 3-hydroxybutyrate and chemical reduction of acetone to 2-propyl alcohol (Gavin0 et al. 1986; Haff and Richard 1977). Another factor that makes determination of acetone unreliable is the increased evaporative loss of acetone from the samples as the time of storage is prolonged (Trotter et al. 1971). Acetone was detected in several brands of heparin (Powell et al. 1985). Therefore, determination of acetone in heparinized blood may give erroneous results if the heparin is contaminated with acetone.

6.2 ENVIRONMENTAL SAMPLES

Some of the analytical methods for determining acetone in environmental samples are reported in Table 6-2. In addition to these methods, personal sampling methods have been developed in Japan for the determination of acetone in the workplaces (Uchida et al. 1990). There is no unique method that can be used for the determination of low levels of acetone in unpolluted environmental samples. As in the case of biological samples, the sensitivity of acetone detection in environmental samples can be enhanced by derivatization. Such a method, which uses 2,4-dinitrophenylhydrazine as a derivatizing agent, has been applied for the determination of extremely low levels of acetone in open ocean sea water (Kieber and Mopper 1990). A new method based on the reaction of mercuric oxide with carbonyl compounds has been applied for the determination of low levels of acetone in unpolluted atmosphere (O'Hara and Singh 1988). A good review of the methods presently used for the determination of acetone in the atmosphere is available (Vairavamurthy et al. 1992). Unlike in biological samples, acetylacetone may not be present in most environmental samples. If acetylacetone is detected in an environmental sample, thermal degradation inside the gas chromatographic system (injection port and column oven) may produce erroneous results unless this interference is eliminated. As in the case of biological samples, proper precautions in sample handling during collection and analysis, and storage of environmental samples should be taken to minimize contamination and evaporative loss. It has been suggested that ambient water containing low levels of acetone be sampled upwind of sources of contamination (e.g., smoke stack or other sources of emissions) and that the operator stand downwind of the samples while withdrawing them (to minimize contamination from operator's breath) (Kieber and Mopper 1990).

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (occupational)	Air passed through charcoal and components disorbed with CS_2	GC-FID (NIOSH method 1300)	0.007 mg/L	No data	NIOSH 1990
Air (occupational)	Air passed through Porapak N and components thermally desorbed	GC-FID	<0.01 ppm (v/v)	110% at 0.52 ppm	Campbell and Moore 1977
Air (occupational)	Air passed through charcoal and components desorbed with CS_2	GC-FID	<0.05 mg/L	74–92%	Otson et al. 1983
Air (ambient)	Air passed through a cryogenic trap and the trapped component injected into GC	GC-RGD	10 ppt	No data	O'Hara and Singh 1988
Air	Air passed through a 1% sodium bisulfite solution and absorbed acetone reacted with alkaline vanilla solution	Spectrophotometry	<0.5 ppm (in solution)	No data	Amlathe and Gupta 1990
Rural air	Air passed through silica gel coated with 2,4-dinitrophenyl-hydrazine and eluted with acetonitrile	HPLC-UV	No data	<90%	Shepson et al. 1991
Water	Sample reacted with alkaline diazotized anthranilic acid solution	Spectrophotometry	0.5 mg/L	98.5–102%	Rahim and Basir 1981

TABLE 6-2. Analytical Methods for Determining Acetone in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Sample reacted with sodium bisulfite	IC/conductivity detection	No data	No data	DuVal et al. 1985
Fresh and seawater	Sample derivatized with 2,4-dinitrophenylhydrazine passed through a C_{18} cartridge and adsorbed compound eluted with acetonitrile	HPLC-UV detection	0.5 nM (0.03 µg/L)	No data	Kieber and Mopper 1990
Waste water, soil or sediment	Sample or sample mixed with reagent water subjected to purge-and-trap	GC-MS (EPA method 8240)	100 µg/L (water) 100 µg/kg (sediment and soil)	No data	EPA 1986
Fresh fruit	Vacuum distillation followed by solvent extraction of pulp	HRGC-MS	No data	No data	Takeoka et al. 1988

CS_2 = carbon disulfide; FID = flame ionization detector; GC = gas chromatography; HPLC = high performance liquid chromatography; HRGC = high resolution gas chromatography; IC = ion chromatography; MS = mass spectrometry; RGD = reduction gas detector; UV = ultraviolet; v/v = volume per volume

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of acetone is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of acetone.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. The concentration of acetone in expired air, blood, and urine can serve as indicators of recent exposure to acetone (Ghittori et al. 1987; Pezzagno et al. 1986; also see Section 2.5.1.). Concentrations of acetone similar to those produced from occupational exposure are also produced in blood and urine as a result of inhalation and ingestion of isopropyl alcohol (may be present as a contaminant in some alcoholic beverages) (Kawai et al. 1990b) and in patients with diabetes mellitus (Dobson et al. 1968; Trotter et al. 1971). Among urine, alveolar air, and blood, the strongest correlation was found between the time-weighted average breathing zone air concentration and urinary acetone level when the concentration of acetone in breathing zone air exceeded 15 ppm (v/v) (Fujino et al. 1992; Kawai et al. 1992). Analytical methods of adequate sensitivities are available for determining acetone in blood, urine, and expired air at background levels in the population and levels at which biological effects occur (Gavin0 et al. 1986; Kobayshi et al. 1983; Phillips and Greenberg 1987; Trotter et al. 1971). Although the precision and accuracy of the analytical methods have not always been reported (e.g., Robayashi et al. 1983), these values are satisfactory in cases where they have been reported (Haff and Reichard 1977; Holm and Lundgren 1984; Mangani and Ninfali 1988; Trotter et al. 1971).

Biological monitoring has not been used to associate acetone exposure levels with specific effects that can be quantified in humans (see Section 2.5.2). Clinical tests for nonspecific effects of acetone exposure (see Section 2.9.2) are available (Johansson et al. 1988; Lupulescu et al. 1972, 1973; Tosti et al. 1988). Since acetone exposure itself can be quantified in biological tissues, there does not appear to be a need to improve existing clinical tests or develop additional test procedures to detect effects of acetone exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining low levels of acetone found in ambient air are available (Ants and Meeks 1981; Cavanagh et al. 1969; O'Hara and Singh 1988; Shepson et al. 1991; Snider and Dawson 1985). Methods are also available for determining low levels of acetone found in natural waters (Kieber and Mopper 1990). The concentrations of acetone found in volatile components of several foods have also been determined (Bartley and Schwede 1989; Day and Anderson 1965; Takeoka et al. 1988). The degradation products formed as a result of photochemical reactions of acetone in air in the presence or absence of nitrogen oxides have been identified (Altshuller and Bufalini 1971; Boule et al. 1987; Hanst and Gay 1983; Meyrahn et al. 1986). However, products from the reaction of acetone with hydroxyl radicals and $O(^3P)$ remain unidentified (Cox et al. 1980; Lee and Timmons 1977), although it has been postulated that methylglyoxal may be the principal product of the reaction with hydroxyl radicals (Altshuller 1991). It would be helpful to determine the products formed from the gas phase reaction of acetone with hydroxyl radicals in order to assess the potential health effect implications of these products.

6.3.2 On-going Studies

No on-going studies that could free the data gap regarding the products formed from the reactions of acetone with atmospheric oxidants (e.g., hydroxyl radicals, $O[^3P]$) were found.

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

7. REGULATIONS AND ADVISORIES

National and State regulations and guidelines are listed in Table 7-1.

An acute-duration inhalation MRL for acetone of 26 ppm was derived. The MRL is based on a LOAEL value of 237 ppm for 4 hours for neurobehavioral effects in humans in an experimental study by Dick et al. (1989). Intermediate and chronic inhalation MRLs of 13 ppm were derived based on a LOAEL value of 1,250 ppm for neurological effects in humans in a 6-week study by Stewart et al. (1975).

An intermediate-duration oral MRL for acetone of 2 mg/kg/day was derived. The MRL is based on a NOAEL value of 200 mg/kg/day for macrocytic anemia in rats in the 13-week drinking water study (Dietz et al. 1991; NTP 1991). The LOAEL was 400 mg/kg/day.

EPA has verified a chronic oral reference dose (RfD) for acetone of 0.1 mg/kg/day (IRIS 1992). The RfD is based on the NOAEL of 100 mg/kg/day for increased liver and kidney weights and nephrotoxicity in rats in the 13-week gavage study by American Biogenics Corp. (1986).

TABLE 7-1. Regulations and Guidelines Applicable to Acetone

Agency	Description	Information	References
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA	750 ppm (1,800 mg/m^3)	OSHA 1989 (29 CFR 1910.1000)
	STEL	1,000 ppm (2,400 mg/m^3)	
b. Other:			
EPA OERR	RQ	5,000 pounds	EPA 1985 (40 CFR 117 and 302)
Guidelines:			
a. Air:			
ACGIH	TLV TWA	750 ppm (1,780 mg/m^3)	ACGIH 1991
	STEL	1,000 ppm (2,380 mg/m^3)	
NIOSH	REL TWA	250 ppm (590 mg/m^3)	NIOSH 1992
b. Other:			
EPA	RfD (oral)	0.1 mg/kg/day	IRIS 1992
	Carcinogen classification	D[a]	IRIS 1992
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		NATICH 1992
Arizona		20.0 mg/m^3 (1-hour average)	
		14.0 mg/m^3 (24-hour average)	
Connecticut		11.8 mg/m^3 (8-hour average)	
Florida:			
(Tampa)		35.6 mg/m^3 (8-hour average)	
(Fort Lauderdale)		36.0 mg/m^3 (8-hour average)	
(Pinella)		35.6 mg/m^3 (8-hour average)	
(Pinella)		8.54 mg/m^3 (24-hour average)	
Massachusetts		0.161 mg/m^3 (24-hour average)	
		0.161 mg/m^3 (annual)	
Maine		3.5 mg/m^3 (24-hour average)	
		0.35 mg/m^3 (annual)	
North Dakota		17.8 mg/m^3 (8-hour average)	
		23.8 mg/m^3 (1-hour average)	
Nevada		42.4 mg/m^3 (8-hour average)	
New York		35.6 mg/m^3 (1-year average)	
South Dakota		11.8 mg/m^3 (8-hour average)	
Texas		5.9 mg/m^3 (30-minute average)	
		0.59 mg/m^3 (annual)	
Virginia		30.0 mg/m^3 (24-hour average)	
Vermont		178 mg/m^3 (8-hour average)	
b. Water:	Drinking water quality standards		FSTRAC 1990
Massachusetts		700 µg/L	
Maryland		3,600 µg/L	
Minnesota		700 µg/L	
New Hampshire		700 µg/L	

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Acetone *(continued)*

Agency	Description	Information	References
STATE *(continued)*			
standards for spent solvents			Treatment CELDS 1992 CaliforniaWaste
waters containing spent acetone	0.05 mg/L		
spent acetone wastes	0.59 mg/L		All other

[a]Not classifiable as to human carcinogenicity

ACGIH = American Conference of Governmental Industrial Hygientists; EPA = Environmental Protection Agency; NIOSH = National Institute for Occupational Safety and Health; OERR = Office of Emergency and Remedial Resonse; OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; RfD = Reference Dose; RQ = Reportable Quantity; STEL = Short-term Exposure Limit; TLV = Threshold Limit Value; TWA = Time-weighted Average

8. REFERENCES

*Abbondandolo A, Bonatti S, Corsi C, et al. 1980. The use of solvents in mutagenicity testing. Mutat Res 79:141-150.

*Abe S, Sasaki M. 1982. SCE as an index of mutagenesis and/or carcinogenesis. In: Sister chromatid exchange. Progress Topics Cytogenetics 2:461-514.

*Abrams EF, Derkics CV, Fong DK, et al. 1975. Identification of organic compounds in effluents from industrial sources. Springfield, VA: Versar Inc. EPA 560/3-75-002.

*ACGIH. 1991. Threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*Adams CW, Bayliss OB. 1968. Histochemistry of myelin. VI. Solvent action of acetone on brain and other lipid-rich tissues. J Histochem 16:115-118.

*Aharonson EF, Menkes H, Gurtner G, et al. 1974. Effect of respiratory airflow rate on removal of soluble vapors by the nose. J Appl Physiol 37:654-657.

*Ahonen I, Schimberg RW. 1988. 2,5-Hexanedione excretion after occupational exposure to nhexane. Br J Ind Med 45:133-136.

*Albertini S. 1991. Reevaluation of the 9 compounds reported conclusive positive in yeast Succharomyces cerevisiae aneuploidy test systems by the gene-tox program using strain D61.M of Succharomyces *cerevisiue.* Mutat Res 260: 165- 180.

*Albertini S, Friederich U, Holderegger C, et al. 1988. The *in vitro* porcine brain tubulin assembly assay: Effects of a genotoxic carcinogen (Aflatoxin Bl), eight tumor promoters and nine miscellaneous substances. Mutat Res 201:283-292.

*Albertoni P. 1884. [The effect and transformations of chemicals *in vivo* in relation to the pathogenicity of acetonemia and diabetes.] Archiv fur Experimentelle Pathologie und Pharmakologie 18:219-241. (German).

Albertoni P, Pisenti G. 1887. On the activity of acetone and acetic acid on the kidneys. Contribution to the pathogenicity of albuminuria and nephritis. Archiv fur Experimentelle Pathologie und Pharmakologie 23:393-413. (German).

*Altshuller AP. 1991. The production of carbon monoxide by the homogeneous NO,-induced photooxidation of volatile organic compounds in the troposphere. Journal of Atmospheric Chemistry 13:155-182.

*Altshuller AP, Bufalini JJ. 1971. Photochemical aspects of air pollution: A review. Environmental Science and Technology 5:39-64.

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*Cited in text

*Altshuller AP, Cohen IR. 1963. Structural effects of the rate of nitrogen dioxide formation in the photooxidation of organic compound-nitric oxide mixtures in air. Int J Air Water Pollut 7:789-797.

*Amacher DE, Paillet SC, Turner GN, et al. 1980. Point mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells. 2. Test validation and interpretation. Mutat Res 72:447-474.

*American Biogenics Corp. 1986. Ninety day gavage study in albino rats using acetone. American Biogenics Corp, Decatur, IL. [Unpublished study to be peer reviewed]

*Amlathe S, Gupta VK. 1990. Spectrophotometric determination of acetone using vanillin. Analyst 115:1385-1387.

*Amoore JE, Hautala E. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 3:272-290.

*Anbar M, Neta P. 1967. A compilation of specific bimolecular rate constant for the reactions of hydrated electrons, hydrogen atoms and hydroxyl radical with inorganic and organic compounds in aqueous solution. Int J Appl Radiat Isot 18:493-523.

Anders MW. 1968. Stimulatory effect of acetone on the activity of microsomal aniline parahydroxylase. In: Gillette JR, ed. Proceedings of the Symposium on Microsomes and Drug Oxidation. New York, NY:Academic Press, 533-540.

*Anselme C, Nguyen K, Burchet A, Mallevialle J. 1985. Characterization of low molecular weight products desorbed from polyethylene tubings. Sci Total Environ 47:371-384.

*Arnold F, Knop G, Ziereis H. 1986. Acetone measurements in the upper troposphere and lower stratosphere implications for hydroxyl radical abundances. Nature 321:505-507.

Arnts RR, Meeks SA. 1981. Biogenic hydrocarbon contribution to the ambient air of selected areas. Atmos Environ 15: 1643-l 65 1.

*Ashley DL, Bonin MA, Cardinali FL, et al. 1992. Determining volatile organic compounds in human blood from a large sample population by using purge and trap gas chromatography/mass spectrometry. Anal Chem 64:1021-1029.

*ATSDR. 1988. Health assessment for Vega Alta public supply wells site: Vega Alta, Puerto Rico, Region 2. CERCLIS no. PRS187147. Agency for Toxic Substances and Disease Registry. Division of Toxicology. 1600 Clifton Road NE, E-29, Atlanta, Georgia. NTIS PA90-139213.

*ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles. Agency for Toxic Substances and Disease Registry. Division of Toxicology. 1600 Clifton Road NE, E-29, Atlanta, Georgia.

*Axelsson G, Luetz C, Rylander R. 1984. Exposure to solvents and outcome of pregnancy in university laboratory employees. Br J Ind Med 41:305-312.

*Babeu L, Vaishnav DD. 1987. Prediction of biodegradability for selected organic chemicals. J Ind Microb 2:107-115.

*Banhegyi G, Garzo T, Antoni F, et al. 1988. Accumulation of phenols and catechols in isolated mouse hepatocytes in starvation or after pretreatment with acetone. Biochem Pharmacol 37:4157-4162.

*Barber ED, Lodge Jr JP. 1963. Paper chromatographic identification of carbonyl compounds as their 2,4-dinitrophenyl hydrazones in automobile exhaust. Anal Chem 35:348-350.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486.

*Barnett CR, Petrides L, Wilson J, et al. 1992. Induction of rat hepatic mixed-function oxidases by acetone and other physiological ketones: Their role in diabetes-induced changes in cytochrome P450 proteins. Xenobiotica 2:1441-1450.

*Barr-Nea LM, Wolman M. 1977. Tumors and amyloidosis in mice painted with crude oil found on bathing beaches. Bull Environ Contam Toxicol 18:385-391.

*Bartley JP, Schwede AM. 1989. Production of volatile compounds in ripening kiwi fruit *(Actinidia chinensis).* 3 Agric Food Chem 37:1023-1025.

*Basler A. 1986. Aneuploidy-inducing chemicals in yeast evaluated by the micronucleus test. Mutat Res 174:11-13.

*Bedding ND, McIntyre AE, Perry R, et al. 1982. Organic contaminants in the aquatic environment. I. Sources and occurrence. Sci Total Environ 25:143-167.

*Bhattacharya SK, Angara RVR, Bishop Jr DF, et al. 1990. Removal and fate of RCRA and CERCLA toxic organic pollutants in wastewater treatment. Cincinnati, OH: U.S. Environmental Protection Agency, Risk Reduction Eng. Laboratory. EPA 600/S2-89-026.

*Boggild MD, Peck RW, Tomson CRV. 1990. Acetonitrile ingestion: Delayed onset of cyanide poisoning due to concurrent ingestion of acetone. Postgrad Med J 66:40-41.

*Bolkova A, Cejkova J. 1983. Changes in alkaline and acid phosphatases of the rabbit cornea following experimental exposure to ethanol and acetone: A biochemical and histochemical study. Graefes Arch Clin Exp Ophthalmol 220:96-99.

*Boule P, Gyuon C, Tissot A, et al. 1987. Specific phototransformation of xenobiotic compounds, chlorobenzenes and halophenols. ACS Symp. Ser. 327. Washington, DC: American Chemical Society, 10-26.

*Boyd AA, Canosa-Mas CE, King AD, et al. 1991. Use of a stopped-flow technique to measure the rate constants at room temperature for reactions between the nitrate radical and various organic species. Journal of the Chemical Society Faraday Transactions 87:2913-2919.

*Brady JF, Li D, Ishizaki H, et al. 1989. Induction of cytochrome P45OIIEl and P450IIBl by secondary acetones and the role of P45OIIEI in chloroform metabolism. Toxicol Appl Pharmacol 100:342-349.

*Brega A, Villa P, Quadrini G, et al. 1991. High-performance liquid chromatographic determination of acetone in blood and urine in the clinical diagnostic laboratory. J Chromatogr 553:249-254.

*Bridie AL, Wolff CJM, Winter M. 1979. BOD and COD of some petrochemicals. Water Res 13:627-630.

*Brondeau MT, Ban M, Bonnet P, et al. 1989. Acetone compared to other ketones in modifying the hepatotoxicity of inhaled 1,2-dichlorobenzene in rats and mice. Toxicol Lett 49:69-78.

*Brown KW, Donnelly KD. 1988. An estimation of the risk associated with the organic constituents of hazardous and municipal waste landfill leachates. Hazardous Waste and Hazardous Materials 5: l-30.

*Brown EM, Hewitt WR. 1984. Dose-response relationships in ketone-induced potentiation of chloroform hepato- and nephrotoxicity. Toxicol Appl Pharmacol 76:437-453.

*Brown WD, Setzer JV, Dick RB, et al. 1987. Body burden profiles of single and mixed solvent exposures. J Occup Med 29:877-883.

*Bruckner JV, Peterson RG. 1981a. Evaluation of toluene and acetone inhalant abuse. I. Pharmacology and pharmacodynamics. Toxicol Appl Pharmacol 61:27-38.

*Bruckner JV, Peterson RG. 1981b. Evaluation of toluene and acetone inhalant abuse. II. Model development and toxicology. Toxicol Appl Pharmacol 61:302-3 12.

*Brugnone F, Perbellini L, Gaffuri E. 1980. Biomonitoring of industrial solvent exposures in workers' alveolar air. Int Arch Occup Environ Health 47:245-261.

*Brugnone F, Perbellini L, Grigolini L. 1978. Solvent exposure in a shoe upper factory. Int Arch Occup Environ Health 42:5 l-62.

*Bruss ML. 1989. Ketogenesis and ketosis. In: Kaneko JJ, ed. Clinical biochemistry of domestic animals. 4th ed. New York, NY: Academic Press, Inc., 86-105.

*Burmaster DE. 1982. The new pollution-groundwater contamination. Environ 24:6-13, 33-36.

*Campbell DN, Moore RH. 1979. The quantitative determination of acrylonitrile, acrolein, acetonitrile and acetone in workplace air. Am Ind Hyg Assoc J 40:904-909.

*Carpenter CP, Smyth Jr HF. 1946. Chemical burns of the rabbit cornea. Am J Ophthalmol 29:1363-1372.

*Carriere V, de Waziers I, Courtois YA, et al. 1992. Cytochrome P450 induction and mutagenicity of 2-aminoanthracene (2AA) in rat liver and gut. Mutat Res 268: 1 l-20.

*Casazza JP, Argiles JM, Veech RL. 1988. Serum levels of acetone in fetal, neonatal, and maternal blood [Abstract]. J Cell Biol 107(pt. 3):206A.

*Casazza JP, Felver ME, Veech RL. 1984. The metabolism of acetone in the rat. Biol Chem 259:231-236.

*Casazza JP, Yun YP, Veech RL, et al. 1990. Serum acetone and P450IIE levels in pregnant rats [Abstract]. Federation American Social Experimental Biology Journal 4:A2244.

*Cavanagh LA, Schadt CF, Robinson E. 1969. Atmospheric hydrocarbon and carbon monoxide measurements at Point Barrow, Alaska. Environmental Science and Technology 3(3):251-257.

*CDC/ATSDR. 1990. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary and immune systems. Atlanta, GA: CDUATSDR Subcommittee on Biomarkers of Organ Damage and Dysfunction, Centers for Disease Control, Agency for Toxic Substances and Disease Registry. Summary report, August 27, 1990.

*CELDS. 1992. Computer Aided Environmental Legislative Data System. February 1992.
Cesaro AN, Pinerolo A. 1947. Percutaneous absorption of acetone. Med Lav 38:384-387.

*Charbonneau M, Brodeur J, du Souich P, et al. 1986a. Correlation between acetone potentiated CCL,-induced liver injury and blood concentrations after inhalation or oral administration. Toxicol Appl Pharmacol 84:286-294.

*Charbonneau M, Couture J, Plaa GL. 1991. Inhalation versus oral administration of acetone: Effect of the vehicle on the potentiation of CCL,-induced liver injury. Toxicol Lett 57:47-54.

*Charbonneau M, Iijima M, C&e MG, et al. 1985. Temporal analysis of rat liver injury following potentiation of carbon tetrachloride hepatotoxicity with ketonic or ketogenic compounds. Toxicology 35:95-111.

*Charbonneau M, Oleskevich S, Brodeur J, et al. 1986b. Acetone potentiation of rat liver injury induced by trichloroethylene-carbon tetrachloride mixtures. Fundam Appl Toxicol 6:654-661.

*Charbonneau M, Perreault F, Greselin E, et al. 1988. Assessment of the minimal effective dose of acetone for potentiation of the hepatotoxicity induced by trichloroethylene-carbon tetrachloride mixtures. Fundam Appl Toxicol 10:431-438.

*Charbonneau M, Tuchweber B, Plaas GL. 1986c. Acetone potentiation of chronic liver injury induced by repetitive administration of carbon tetrachloride. Hepatology 6:694-700.

*Chatfield RB, Gardner EP, Calvery JG. 1987. Sources and sinks of acetone in the troposphere: Behavior of reactive hydrocarbons and a stable product. Journal of Geophysical Research 92:4208-4216.

*Chatterton CC, Elliott RB. 1946. Acute acetone poisoning from leg casts of a synthetic plaster substitute. JAMA 130:1222-1223.

*Chen T, Kavanagh TJ, Chang CC, et al. 1984. Inhibition of metabolic cooperation in Chinese hamster V79 cells by various organic solvents and simple compounds. Cell Biol Toxicol 1: 155-171.

*Chentanez T, Tantrarungroj K, Sadavongvivad C. 1987. Correlation between positive chronotropic effect and norepinephrine release induced by acetone in the rat right atrium. Toxicol Lett 37:183-193.

*Cheung ST, Lin WN. 1987. Simultaneous determination of methanol, ethanol, acetone, isopropanol and ethylene glycol in plasma by gas chromatography. Journal of Chromatography and Biomedical Applications 414:248-250.

*Chieli E, Saviozzi M, Puccini P, et al. 1990. Possible role of the acetone-inducible cytochrome P-450IIEl in the metabolism and hepatotoxicity of thiobenzamide. Arch Toxicol 64(2):122-127.

*Chou WL, Speece RE, Siddiqi RH. 1979. Acclimation and degradation of petrochemical wastewater components by methane fermentation. Biotechnol Bioeng Symp 8:391-414.

Clark H, Powis H. 1974. Effect of acetone administered *in vivo* upon hepatic microsomal drug metabolizing activity in the rat. Biochem Pharmacol 23:1015-1019.

*CMR. 1987. Chemical Profile: Acetone. New York, NY: Chemical Marketing Reports, Schnell Publishing Co., Inc., 67. September 21, 1987.

*CMR. 1990. Chemical Profile: Acetone. New York, NY: Chemical Marketing Reports, Schnell Publishing Co., Inc., 67. July 30, 1990.

*Coleman DL. 1980. Acetone metabolism in mice: Increased activity in mice heterozygous for obesity genes. Proc Nat1 Acad Sci 290-293.

*Coleman EC, Ho C, Chang SS. 1981. Isolation and identification of volatile compounds from baked potatoes. J Agric Food Chem 29:42-48.

*Coleman WE, Lingg RD, Melton RG. 1976. The occurrence of volatile organics in five drinking water supplies using gas chromatography/mass spectrometry. In: Keith L, ed. Analysis and identification of organic substances in water. Ann Arbor, MI: Ann Arbor Science, 305-327.

*Collander R. 1951. The partition of organic compounds between higher alcohols and water. Acta Chem Stand 5:774-780.

*Conkle JP, Camp BJ, Welch BE. 1975. Trace composition of human respiratory gas. Arch Environ Health 30:290-295.

*Corwin JR. 1969. Volatile oxygen-containing organic compounds in sea water: Determination. Bulletin of Marine Science 19:504-509.

*Cox RA, Derwent RG, Williams MR. 1980. Atmospheric photooxidation reactions: Rates, reactivity, and mechanism for reaction of organic compounds with hydroxyl radicals. Environmental Science and Technology 14:57-61.

*Cox RA, Patrick KF, Chant SA. 1981. Mechanism of atmospheric photooxidation of organic compounds. Reactions of alkoxy radicals in oxidation of n-butane and simple ketones. Environmental Science and Technology 15:587-592.

*CRISP. 1993. CRISP data base. National Institutes of Health. April 1993.

*Cunningham C, Gold B. 1992. Endogenous DNA methylation: The effect of cytochrome P45OIIEl inducers [Abstract]. In: Proceedings of the 83rd Annual Meeting of the American Association for Cancer Research, San Diego, CA, May 20-23, 1992, 33:A813.

*Cunningham J, Sharkawi M, Plaa GL. 1989. Pharmacological and metabolic interactions between ethanol and methyl n-butyl ketone, methyl isobutyl ketone, methyl ethyl ketone, or acetone in mice. Fundarn Appl Toxicol 13:102-109.

*Datta RK, Rao KN. 1979. Kinetics of reactions of singlet molecular oxygen (1.&G) with organic compounds. Indian J Chem 18A: 102-105.

*Day EA, Anderson DF. 1965. Gas chromatography and mass spectral identification of natural components of the aroma fraction of blue cheese. J Agric Food Chem 13:2-4.

*De Ceaurriz J, Micillino JC, Marignac B, et al. 1984. Quantitative evaluation of sensory irritating and neurobehavioral properties of aliphatic ketones in mice. Food Chem Toxicol 22:545-549.

*De Flora S. 1981. Study of 106 organic and inorganic compounds in the SuZmoneZZulmicrosome test. Carcinogenesis 2:283-298.

*De Flora S, Zanacchi P, Camoirano A, et al. 1984. Genotoxic activity and potency of 135 compounds in the Ames reversion test and in a bacterial DNA-repair test. Mutat Res 133:161-198.

*De Marini DM, Lawrence BK, Brooks HG, et al. 1991. Compatibility of organic solvents with the microscreen prophage-induction assay: Solvent mutagen interactions. Mutat Res 263:107-l 13.

*DePass LR, Ballantyne B, Fowler EH. et al. 1989. Dermal oncogenicity studies on two methoxysilanes and two ethoxysilanes in male C3H mice. Fundam Appl Pharmacol 12:579-583.

*DeWalle FB, Chian ESK. 1981. Detection of trace organics in well water near a solid waste landfill. J Am Water Works Assoc 73:206-211.

*DeWalle FB, Kalman DA, Norman D, et al. 1985. Determination of toxic chemicals in effluent from household septic tanks. Cincinnati, OH: U.S. Environmental Agency. EPA 600/S2-85-050.

*Dick RB, Brown WD, Setzer JV, et al. 1988. Effects of short duration exposures to acetone and methyl ethyl ketone. Toxicol Lett 43:31-49.

*Dick RB, Setzer JV, Taylor BJ, et al. 1989. Neurobehavioral effects of short duration exposures to acetone and methyl ethyl ketone. Br J Ind Med 46: 1 1 l- 121.

*Dietz DD, Leininger JR, Rauckman EJ, et al. 1991. Toxicity studies of acetone administered in the drinking water of rodents. Fundam Appl Toxicol 17:347-360.

*Dilling WL. 1982. Atmospheric environment. In: Conway RA, ed. Environmental risk analysis for chemicals. New York, NY: Van Nostrand Reinhold Co., 154-197.

*Dimitriades B, Joshi SB. 1977. Application of reactivity criteria in oxidant-related emission control in the USA. EPA 600/3-77-Ollb. NTIS PB264-233, 705-711.

*Ding XX, Coon MJ. 1990. Induction of cytochrome P-450 isozyme 3a (P-45OIIEl) in rabbit olfactory mucosa by ethanol and acetone. Drug Metab Dispos 18742-745.

*DiPaolo JA, Donovan P, Nelson R. 1969. Quantitative studies on *in vitro* transformation by chemical carcinogens. J Nat1 Cancer Inst 42867-874.

*DiVincenzo GD, Yanno FJ, Astill BD. 1973. Exposure of man and dog to low concentrations of acetone vapor. Am Ind Hyg Assoc J 34:329-336.

*Dobson HL, Shaffer R, Burns R. 1968. Accuracy of urine testing for sugar and acetone by hospital ward personnel. Diabetes 17:281-285.

*Dowty BJ, Laseter JL, Storer J. 1976. The transplacental migration and accumulation in blood of volatile organic constituents. Pediatr Res 10:696-701.

Drexler H, Schaller K-H, Weber A, et al. 1993. Skin prick tests with solutions of acid anhydrides in acetone. Int Arch Allergy Appl Immunol 100:25 l-255.

*Duval DL, Rogers M, Fritz JS. 1985. Determination of aldehydes and acetone by ion chromatography. Anal Chem 57:1583-1586.

*Egle Jr JL. 1973. Retention of inhaled acetone and ammonia in the dog. Am Ind Hyg Assoc J 34:533-539.

*EHRT. 1987. Screening of priority chemicals for reproductive hazards: Benzethonium chloride (CAS No. 121-54-O); 3-ethoxy-1-propanol (CAS No. 111-35-3); acetone (CAS No. 67-64-l). Environmental Health Research and Testing, Inc. Cincinnati, OH. NTIS PB89-139083.

Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environmental Science and Technology 15(1):30-38.

*Elovaara E, Engstrom K, Nakajima T, et al. 1991. Metabolism of inhaled styrene in acetonephenobarbital and 3-methylcholanthrene-pretreated rats: Stimulation and stereochemical effects by induction of cytochromes P45OIIE1, P450IIB and P450IA. Xenobiotica 21:65 l-662.

*Elovaara E, Vainio H, Aitio A. 1990. Pulmonary toxicity of inhaled styrene in acetone-, phenobarbital- and 3-methylcholanthrene-treated rats. Arch Toxicol 64:365-369.

*EPA. 1985. Environmental Protection Agency. 40 CFR Parts 117 and 302. Notification requirements: Reportable quantity adjustments: Final rule and proposed rule. Federal Register 50:13456-13522.

*EPA. 1986. Test method for evaluating solid waste. Vol. 18: Laboratory manual of physical/chemical method (SW-846), 3rd ed. Washington, DC: Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency.

*EPA. 1988a. Environmental Protection Agency. Prohibitions on land disposal. 40 CFR 268.30, 268.40 and 268.41.

*EPA. 1988b. Superfund record of decision: Summit National, OH. First remedial action. U.S. Environmental Protection Agency, Washington, DC. EPA/ROD/R05-88/068. NTIS PB89 225908/AS.

EPA. 1988. Updated health effects assessment for acetone. Cincinnati, OH: Oft-ice of Health and Environmental Assessment, Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency. ECAO-CIN-HO16a.

*EPA. 1989. Compilation and speciation of national emissions factors for consumer/commercial solvent use information compiled to support urban air toxics assessment studies. U.S. Environmental Protection Agency, Research Triangle Park, NC. EPA/450/2-89/008. NTIS PB89-207203.

*EPA. 1990. Interim methods for development of inhalation reference doses. U.S. Environmental Protection Agency. EPA/600/8-90/066A.

*EPA. 1991a. Alphq,-globulin: association with chemically induced renal toxicity and neoplasia in the male rat. Risk Assessment forum U.S. Environmental Protection Agency, Washington, DC. EPA/625/3-9 l/O1 9F.

*EPA. 1991b. Environmental Protection Agency. Hazardous waste injection restriction. Federal Register 55:3876.

*Ettiinger MB. 1956. Biochemical oxidation characteristics of stream-pollutant organics. Industrial Engineering Chem 48:256-259.

Farquharson TA, Stock BH. Modified response of hepatic microsomes from rats administered polar aprotic solvents. Australian Journal of Pharmaceutical Sciences 4:ll l-l 15.

*Fastlich E. 1976. Detection of volatile solvents in gastric contents by gas phase infrared spectrophotometry. J Assoc Off Anal Chem 59:130-133.

*FEDRIP. 1992. Federal Research in Progress. February 1992.

*Fiserova-Bergerova V, Diaz ML. 1986. Determination and prediction of tissue-gas partition coefficients. Int Arch Occup Environ Health 58:75-87.

*Fisher P. 1951. The role of the ketone bodies in the etiology of diabetic coma. Am J Med Sci 221:384-397.

*Fitzpatrick LJ, Claire D’AC. 1947. Acute acetone poisoning (resulting from synthetic plaster substitute in spica cast). Anesth Analg 26:86-87.

*Folland DS, Shaffner W, Grinn HE, et al. 1976. Carbon tetrachloride toxicity potentiated by isopropyl alcohol: Investigation of an industrial outbreak. J Am Med Assoc 26: 1853-1856.

*Freeman AE, Weisburger EK, Weisburger JH, et al. 1973. Transformation of cell cultures as an indication of the carcinogenic potential of chemicals. J Nat1 Cancer Inst 51:799-808.

*Freeman JJ, Hayes EP. 1985. Acetone potentiation of acute acetonitrile toxicity in rats. J Toxicol Environ Health 15:609-621.

*Freeman JJ, Hayes EP. 1988. Microsomal metabolism of acetonitrile to cyanide. Biochem Pharmacol 37:1153-l 159.

*FSTRAC. 1990. Summary of State and Federal Drinking Water Standards and Guidelines. Chemical Communication Subcommittee, Federal-State Toxicology and Regulatory Alliance Committee. February 1990.

*Fujiki M, Tajimgi S, Kitamura E, et al. 1978. Simulation studies of degradation of chemicals in the environment; simulation studies of degradation of chemicals in the atmosphere. Chemical Res. report no. l/1978. Tokyo, Japan: Office of Health Studies, Environment Agency Japan,

*Fujino A, Satoh T, Takebayashi T, et al. 1992. Biological monitoring of workers exposed to acetone in acetate fibre plants. Br J Ind Med 49:654-657.

*Fukabori S, Nakaaki K, Tada 0. 1979. [On the cutaneous absorption of acetone.] J Science of Labour 55: 525-532. (Japanese)

*Furrier RL, Neville ED, Talarico KF, et al. 1972. A common modality of action of simulated space stresses on the oxidative metabolism of ethyl morphine, aniline and p-nitroanisole by male rat liver. Toxicol Appl Pharmacol 21:569-581.

*Gamis AS, Wasserman GS. 1988. Acute acetone intoxication in a pediatric patient. Pediatr Emerg Care 4:24-26.

Garcia CR, Geller I, Kaplan HL. 1978. Effects of ketones on lever-pressing behavior of rats. Proc West Pharmacol Sot 21:433-438.

*Gavin0 VC, Vinet B, David F, et al. 1986. Determination of the concentration and specific activity of acetone in biological fluids. Anal Biochem 52:256-261.

*Gaudy Jr AF, Turner BG, Pusztaszeri S. 1963. Biological treatment of volatile waste components. J Water Pollut Contr Fed 35:75-93.

*Gautheron P, Dukic M, Alix D, et al. 1992. Bovine cornea1 opacity and permeability test: An *in vitro* assay of ocular irritancy. Fundam Appl Toxicol 18442-449.

*Gavin0 VC, Somma J, Philbert L, et al. 1987. Production of acetone and conversion of acetone to acetate in the perfused rat liver. J Biol Chem 262:6735-6740.

*Geller I, Gause E, Kaplan H, et al. 1979a. Effects of acetone, methyl ethyl ketone and methyl isobutyl ketone on a match-to-sample task in the baboon. Pharmacol Biochem Behav 11:401-406.

*Geller I, Hartmann RJ, Randle SR, et al. 1979b. Effects of acetone and toluene vapors on multiple schedule performance of rats. Pharmacol Biochem Behav 11:395-399.

*Gerhold RM, Malaney GW. 1966. Structural determinants in the oxidation of aliphatic compounds by activated sludge. J Water Pollut Control Fed 38562-579.

*Gervasi PG, Puccini P, Longo V, et al. 1991. Role of the acetone inducible P-450IIEl In the deethylation of diethylnitrosamine in hamster. In: Witmer CM, Snyder RR, Jollow DJ et al. eds. Vol. 283: Biological reactive intermediates IV: Molecular and cellular effects and their impact on human health. Fourth International Symposium for Advances in Experimental Medicine and Biology, Tucson, AR, Jan. 14-17, 1990. New York, NY: Plenum Publishing Corp., 285-286, 287.

*Ghittori S, Imbriani M, Pezzagno G, et al. 1987. The urinary concentration of solvents as a biological indicator of exposure: Proposal for the biological equivalent exposure limit for nine solvents. Am Ind Hyg Assoc J 48:786.

*Gichner T, Veleminsky J. 1987. The organic solvents acetone, ethanol and dimethylformamide potentiate the mutagenic activity of N-methyl-N'-nitrosoguanidine, but have no effect on the mutagenic potential of N-methyl-N-nitro-N-nitrosourea. Mutat Res 192:31-35.

*Giroux D, Lapointe G, Baril M. 1992. Toxicological index and the presence in the workplace of chemical hazards for workers who breast-feed infants. Am Ind Hyg Assoc J 53:471-474.

*Gitelson S, Werczberger A, Herman JR. 1966. Coma and hyperglycemia following drinking of acetone. Diabetes 15:810-811.

*Glatt H, DeBalle L, Oesch F. 1981. Ethanol- or acetone-pretreatment of mice strongly enhances the bacterial mutagenicity of dimethylnitrosamine in assays mediated by liver subcellular fraction, but not in host-mediated assays. Carcinogenesis 2:1057-1067.

*Glowa JR, Dews PB. 1987. Behavioral toxicology of volatile organic solvents. IV. Comparisons of the rate-decreasing effects of acetone, ethyl acetate, methyl ethyl ketone, toluene, and carbon disulfide on schedule-controlled behavior of mice. J Am College Toxicol 6:461-469.

*Goldberg ME, Johnson HE, Pozzani UC, et al. 1964. Effect of repeated inhalation vapors of industrial solvents on animal behavior. Am Ind Hyg Assoc J 25:369-375.

*Goldfrank LR, Flomenbaum NE, Lewin NA, et al. 1990. Goldfrank's toxicologic emergencies. 4th ed. Norwalk, CN: Appleton and Lange, 760-767.

*Gordon AW, Gordon M. 1981. Analysis of volatile organic compounds in a textile finishing plant effluent. Trans Kentucky Academy of Science 42:149-157.

*Goss K-U. 1992. Effects of temperature and relative humidity on the sorption of organic vapors on quartz sand. Environmental Science and Technology 26:2287-2294.

*Gould JP, Ramsey RE, Giabbai M, et al. 1983. Formation of volatile haloorganic compounds in the chlorination of municipal landfill leachates. In: Water Chlorination: Environmental Impact and Health Effects, Vol. 4. Ann Arbor, MI: Ann Arbor Science Publ, 525-539.

*Graedel TE. 1978. Chemical compounds in the atmosphere. New York, NY: Academic Press, 7, 182.

*Graedel TE, Hawkins DT, Claxton LD. 1986. Atmospheric chemical compounds: Sources, occurrence, and bioassay. New York, NY: Academic Press, Inc., 263.

Grant WM. 1986. Toxicology of the eye. Springfield, IL: Charles C. Thomas, 41-42.

*Green WJ, Lee GF, Jones RA, et al. 1983. Interaction of clay soils with water and organic solvents: Implications for the disposal of hazardous wastes. Environmental Science and Technology 17:278-282.

Grey TC, Shrimpton DH. 1967. Volatile components of raw chicken breast muscle. Br Poultry Sci 8:23-33.

*Grosjean D, Wright B. 1983. Carbonyls in urban fog, ice fog, cloudwater and rainwater. Atmos Environ 17:2093-2096.

*Guntakatta ME, Matthews EJ, Rundell JO. 1984. Development of a mouse embryo limb bud cell culture system for the estimation of chemical teratogenic potential. Tertogen Carcinogen Mutagen 4:349-364.

Haag SM, Sipes IG. 1980. Differential effects of acetone or Aroclor 1254 pretreatment on the microsomal activation of dimethylnitrosamine to a mutagen. Mutat Res 74:431-438.

*Haddad LM, Winchester JF. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: WB Saunders Company, 1257-1259.

*Haff AC, Reichard Jr GA. 1977. A method for estimation of acetone radioactivity and concentration in blood and urine. Biochem Med 18:308-314.

*Haggard HW, Greenberg LA, Turner JM. 1944. The physiological principles governing the action of acetone together with determination of toxicity. Journal of Industrial Hygiene and Toxicology 26:133-151.

*Hahn WJ, Werschulz PP. 1986. Evaluation of alternatives to toxic organic paint strippers. Washington, DC: U.S. Environmental Protection Agency. NTIS PB219-177/AS.

*Hall Jr LW, Hall WS, Bushong SJ, et al. 1987. In situ striped bass (Morone Saxatilis) contaminant and water quality studies in the Potomac River. Aquat Toxicol 10:73-99.

*Hallbourg RR, Delfino JJ, Miller W. 1992. Organic priority pollutants in groundwater and surface water at three landfills in north central Florida. Water Air Soil Pollut 65:307-322.

*Hallier E, Filser JG, Bolt HM. 1981. Inhalation pharmacokinetics based on gas uptake studies. II. Pharmacokinetics of acetone in rats. Arch Toxicol 47:293-304.

*Hanst PL, Gay Jr BW. 1983. Atmospheric oxidation of hydrocarbons: Formation of hydroperoxides and peroxyacids. Atmos Environ 17:2259-2265.

*Harris LC, Jackson RH. 1952. Acute acetone poisoning caused by setting fluid for immobilizing casts. Br Med J 2:1024-1026.

*Hatfield R. 1957. Biological oxidation of some organic compounds. Ind Eng Chem 49:192-196.

*Hawthorne SB, Sievers RE. 1984. Emission of organic air pollutants from shale oil wastewaters. Environmental Science and Technology 18:483-490.

*HAZDAT. 1992. Hazardous Substances Database. Agency for Toxic Substances and Disease Registry (ATSDR), Office of External Affairs, Exposure and Disease Registry Branch, Atlanta, GA.

*Hellman TM, Small FH. 1974. Characterization of the odor properties of 101 petrochemicals using sensory methods. JAPCA 24:979-982.

*Hetenyi Jr G, Ferrarotto C. 1985. Gluconeogenesis from acetone in starved rats. Biochem J 231:151-155.

*Hetu C, Joly JG. 1988. Effects of chronic acetone administration on ethanol-inducible monooxygenase activities in the rat. Biochem Pharmacol 37:421-426.

*Heukelekian H, Rand MC. 1955. Biochemical oxygen demand of pure organic compounds. J Water Pollut Control Assoc 27:1040-1053.

*Hewitt WR, Plaa GL. 1983. Dose-dependent modification of l,l-dichloroethylene toxicity by acetone. Toxicol Lett 16: 145- 152.

Hewitt LA, Ayotte P, Plaa GL. 1986. Modifications in rat hepato biliary function following treatment with acetone, 2-butanone, 2-hexanone, Mirex or Chlorodecone and subsequently exposed to chloroform. Toxicol Appl Pharmacol 83:465-473.

*Hewitt LA, Valiquette C, Plaa GL. 1987. The role of biotransformation-detoxication in acetone-, 2-butanone-, and 2-hexanone-potentiated chloroform-induced hepatotoxicity. Can J Physiol Pharmacol 65:2313-2318.

*Hewitt WR, Brown EM, Plaa GL. 1983. Acetone-induced potentiation of trihalomethane toxicity in male rats. Toxicol Lett 16:285-296.

*Hewitt WR, Miyajima H, C8tC MG, et al. 1980. Acute alteration of chloroform-induced hepato- and nephrotoxicity by n-hexane, methyl n-butyl ketone and 2,5-hexanedione. Toxicol Appl Pharmacol 53:230-248.

Hewitt WR, Miyajima H, C6tC MG, et al. 1980. Modification of haloalkane-induced hepatotoxicity by exogenous ketones and metabolic ketosis. Fed Proc 13:3118-3123.

*Hift W, Pate1 PL. 1961. Acute acetone poisoning due to a synthetic plaster cast with a discussion of acetone metabolism. South African Medical Journal 35:246-250.

*Hites RA, Lopez-Avila V. 1980. Sedimentary accumulations of industrial organic compounds discharged into a river system. In: Baker RA, ed. Contaminants and sediments, Vol. 1: Fate and transport case studies, modeling, toxicity. Ann Arbor, MI: Ann Arbor Science.

*Hodgkin JH, Galbraith MN, Chong YK. 1982. Combustion products from burning polyethylene. J Macromol Sci Chem 17:35-43.

*Hodgson AT, Daisey JM, Grot RA. 1991. Sources and source strengths of volatile organic compounds in a new office building. J Air Waste Manage Assoc 41:1461-1468.

*Hodgson AT, Garbesi K, Sextro RG, et al. 1992. Soil-gas contamination and entry of volatile organic compounds into a house near a landfill. J Air Waste Manage Assoc 42:277-283.

*Hodgson AT, Wooley JD, Daisey JM. 1993. Emissions of volatile organic compounds from new carpets measured in a large-scale environmental chamber. J Air Waste Manage Assoc 42:316-324.

*Helm S, Lundgren E. 1984. A purge-and-trap method for the analysis of acetone in biological tissues. Anal Biochem 136:157-160.

*Hong J, Yang CS. 1985. The nature of microsomal N-nitrosodimethylamine demethylase and its role in carcinogen activation. Carcinogenesis 6: 1805- 1809.

*Hong J-Y, Pan J, Dong Z, et al. 1987. Regulation of N-nitrosodimethylamine demethylase in rat liver and kidney. Cancer Res 47:5948-5953.

*HSDB. 1992. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. February 1992.

*Hu JJ, Hong JY, Lea MA, et al. 1990. Cytochrome P450IIEl in rat morris hepatomas [Abstract]. Proc Annu Meet Am Assoc Cancer Res 3 1 :A766.

*Hwang HM, Hodson RE, Lewis DL. 1989. Microbial degradation kinetics of toxic organic chemicals over a wide range of concentrations in natural aquatic systems. Environmental Toxicology and Chemistry 8:67-74.

Hyland R, Gescher A, Thummel K, et al. 1992. Metabolic oxidation and toxification of N-methylformamide catalyzed by the cytochrome P450 isoenzyme CYP2El. Mol Pharmacol 41:259-266.

*IRIS. 1992. Integrated Risk Information System. U.S. Environmental Protection Agency, Washington, DC. January 30, 1992.

*Ishidate Jr M, Sofuni T, Yoshikawa K, et al. 1984. Primary mutagenicity screening of food additives currently used in Japan. Food Chem Toxicol 22:623-636.

*Isidorov VA, Zenkevich, IG, Ioffe BV. 1985. Volatile organic compounds in the atmosphere of forests. Atmos Environ 19:1-8.

*Isidorov VA, Zenkevich IG, Ioffe BV. 1990. Volatile organic compounds in solfataric gases. J Atmos Chem 10:329-340.

*Iversen OH, Paulsen JE, Schjolberg A. 1981. The time needed for normalization of hairless mouse epidermis after treatment with twice weekly topical skin applications of 10 nmol 12-0-tetradecanoylphorbol-13-acetate in acetone, or acetone alone, for 18 weeks: A morphologic and cell kinetic study. Carcinogenesis 2:1353-1358.

*Iversen, OH, Ljunggren S, Olsen WM. 1988. The early effects of a single application of acetone and various doses of 7,1Zdimethylbenz(alpha)anthracene on CD-l and hairless mouse epidermis: A cell kinetic study of so-called initiation and complete carcinogenesis (initiation plus promotion) in chemical skin tumor induction. APMIS Suppl 2:7-80.

*Jaeger RJ, Conolly RB, Reynolds ES. 1975. Biochemical toxicology of unsaturated halogenated monomers. Environ Health Perspect 11:121-128.

*Jakubowski M, Wieczorek H. 1988. The effects of physical effort on pulmonary uptake of selected organic compound vapours. Pol J Occup Med 1:62-71.

*Jansson BO, Larsson BT. 1969. Analysis of organic compounds in human breath by gas chromatography-mass spectrometry. J Lab Clin Med 74:961-966.

*Jarke FH, Dravnieks A, Gordon SM. 1981. Organic contaminants in indoor air and their relation to outdoor contaminants. ASHRAE Trans 87:153-166.

*Jeffery EH, Arndt K, Haschek WM. 1991. The role of cytochrome P450IIEl in bioactivation of acetaminophen in diabetic and acetone-treated mice. In: Witmer CM, Snyder RR, Jollow DJ et al. eds. Vol. 283: Biological reactive intermediates IV: Molecular and cellular effects and their impact on human health. Fourth International Symposium for Advances in Experimental Medicine and Biology, Tucson, AR, Jan. 14-17, 1990. New York, NY: Plenum Publishing Corp., 249-251.

*Jenney EH, Pfeiffer CC. 1958. The convulsant effect of hydrazides and the antidotal effect of anticonvulsants and metabolites. J Pharmacol Exp Ther 122: 1 lo- 123.

*Johansson I, Ingelman-Sundberg M. 1988. Benzene metabolism by ethanol-, acetone- and benzeneinducible cytochrome P-450 (IIEl) in rat and rabbit liver microsomes. Cancer Res 48:5837-5390.

*Johansson I, Ekstriim, Puzyeki D, et al. 1988. Ethanol-, fasting- and acetone-inducible cytochromes P-450 in rat liver: Regulation and characteristics of enzymes belonging to the IIB and IIE gene subfamilies. Biochemistry 27:1925-1934.

*Johansson I, Eliasson E, Norsten C, et al. 1986. Hydroxylation of acetone by ethanol- and acetoneinducible cytochrome P-450 in liver microsomes and reconstituted membranes. FEBS Lett 196:59-64.

*Jones AW. 1987. Breath-acetone concentrations in fasting healthy men: Response of infrared breathalcohol analyzers. J Anal Toxicol 11:67-69.

*Jones AW. 1988. Breath acetone concentrations in fasting male volunteers: Further studies and effect of alcohol administration. J Anal Toxicol 12:75-79.

*Jonsson A, Persson KA, Grigoriadis V. 1985. Measurements of some low molecular-weight oxygenated, aromatic, and chromated hydrocarbons in ambient air and in vehicle emissions. Environment International 11:383-392.

*Jungclaus GA, Lopez-Avila V, Hites RA. 1978. Organic compounds in an industrial waste water: A case study of their environmental impact. Environmental Science and Technology 12:88-96.

*Juttner F. 1986. Analysis of organic compounds (VOC) in the forest air of southern Black Forest. Chemosphere 15:985-992.

*Kane LE, Dombroske R, Alarie V. 1980. Evaluation of sensory irritation from some common industrial solvents. Am Ind Hyg Assoc J 41:451-455.

*Kawachi T, Yahagi T, Kada T, et al. 1980. Cooperative programme on short-term assays for carcinogenicity in Japan. In: Montesano R, ed. Molecular and cellular aspects of carcinogen screening tests. Lyons, France: World Health Organization, 323-330.

*Kawai T, Yasugi T, Horiguchi S, et al. 1990b. Biological monitoring of occupational exposure to isopropyl alcohol vapor by urinalysis for acetone. Int Arch Occup Environ Health 62:409-413.

*Kawai T, Yasugi T, Mizunuma K, et al. 1992. Curvi-linear relation between acetone in breathing zone air and acetone in urine among workers exposed to acetone vapor. Toxicol Lett 62:85-91.

*Kawai T, Yasugi T, Uchida Y, et al. 1990a. Urinary excretion of unmetabolized acetone as an indicator of occupational exposure to acetone. Int Arch Occup Environ Health 62:165-170.

*Keith LH, Garrison AW, Allen FR, et al. 1976. Identification of organic compounds in drinking water for thirteen U.S. cities. In: Keith LH, ed. Identification and Analysis of Organic Pollutants in Water. Ann Arbor, MI: Ann Arbor Press, 329-373.

Kennedy GL Jr, Graepel GJ. 1991. Acute toxicity in the rat following either oral or inhalation exposure. Toxicol Lett 56:317-326.

*Khalil MAK, Rasmussen RA. 1992. Forest hydrocarbon emissions: Relationships between fluxes and ambient concentrations. J Air Waste Manage Assoc 42:810-813.

*Kieber RJ, Mopper K. 1990. Determination of picomolar concentrations of carbonyl compounds in natural waters, including seawater, by liquid chromatography. Environmental Science and Technology 24:1477-1481.

*Kim SG, Shehin SE, States JC, et al. 1990. Evidence for increased translational efficiency in the induction of P450IIEl by solvents: Analysis of P45OIIEl mRNA polyribosomal distribution. Biochem Biophys Res Commun 172:767-774.

*Kimura ET, Ebert DM, Dodge PW. 1971. Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol Appl Pharmacol 19:699-704.

*Kimura M, Shimosawa M, Kobayashi K, et al. 1986. Acetoacetate decarboxylase activity of plasma components. Japanese Journal of Clinical Chemistry 15:37-43.

*Kinlin TE, Muralidhara R, Pittet AO, et al. 1972. Volatile components in roasted filberts. J Agric Food Chem 20:1021.

*Kinsler S, Levi PE, Hodgson E. 1990. Relative contributions of the cytochrome P450 and flavincontaining monooxygenases to the microsomal oxidation of phorate following treatment of mice with phenobarbital, hydrocortisone, acetone, and piperonyl butoxide. Pestic Biochem Physiol 37: 174-181.

*Kitchin KT, Ebron MT. 1984. Further development of rodent who embryo culture: Solvent toxicity and water insoluble compound delivery system. Toxicology 30:45-57.

*Kleindienst TE, Shepson PB, Edney EO, et al. 1986. Wood smoke: Measurement of the mutagenic activities of its gas and particulate-phase photooxidation products. 20:493-501.

*Knoeppel H, Shauenburg H. 1989. Screening of household products for the emission of volatile organic compounds. Environment International 15:413-418.

*Kobayashi K, Okada M, Yasuda Y, et al. 1983. A gas chromatographic method for the determination of acetone and acetoacetic acid in urine. Clin Chim Acta 133:223-226.

*Kobusch AB, Plaa GL, DuSonich P. 1989. Effects of acetone and methyl n-butyl ketone on hepatic mixed function oxidase. Biochem Pharmacol 38:3461-3467.

Koehler AE, Windsor E, Hill E. 1941. Acetone and acetoacetic acid studies in man. J Biol Chem 140:81 l-825.

*Koeslag JH, Noakes TD, Sloan AW. 1980. Post-exercise ketosis. J Physiol (Lond) 301:79-90.

*Kohli RP, Kishor K, Dua PR, et al. 1967. Anticonvulsant activity of some carbonyl containing compounds. Indian J Med Res 55:1221-1225.

*Koop DR, Casazza JP. 1985. Identification of ethanol-inducible P-450 isozyme 3a as the acetone and acetol monooxygenase of rabbit microsomes. J Biol Chem 260: 13607-13612.

*Koop DR, Chernosky A, Brass EP. 1991. Identification and induction of cytochrome P450 2El in rat Kupffer cells. J Pharmacol Exp Ther 258:1072-1076.

*Koop DR, Laethem CL, Schnier GG. 1989. Identification of ethanol-inducible P450 3a(P450IIEl) as a benzene and phenol hydroxylase. Toxicol Appl Pharmacol 98:278-288.

*Koorevaar G, Van Stekelenburg GJ. 1976. Mammalian acetoacetate decarboxylase activity: Its distribution in subfractions of human albumin and occurrence in various tissues of the rat. Clin Chim Acta 71:173-183.

*Kosugi K, Chandramouli V, Kumaran K, et al. 1986a. Determinants in the pathways followed by the carbons of acetone in their conversion to glucose. J Biol Chem 261:13179-13181.

*Kosugi K, Scofield RF, Chandramouli V, et al. 1986b. Pathways of acetone's metabolism in the rat. J Biol Chem 162:3952-3957.

*Kraner J, Lasker J, Ray S, et al. 1991. Induction of P450IIEl by acetone in cultured rabbit hepatocytes involves increased protein synthesis. FASEB J 5:A1515.

*Krasavage WJ, O'Donoghue JL, Divencenzo GD. 1982. Ketone. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology, Vol. 2C, 3rd ed. New York, NY: John Wiley and Sons, 4709-4800.

*Krotoszynski B. 1977. Characterizing of human expired air: A promising investigative and diagnostic technique. J Chromatgr Sci 15:239-244.

*Krotoszynski BK, Bruneau GM, O'Neill HJ. 1979. Measurement of chemical inhalation exposure in urban population in the presence of endogenous effluents. J Anal Toxicol 3:225-234.

*Kubinski H, G.E. Gutske and Z.O. Kubinski. 1981. DNA-cell-binding (DCB) assay for suspected carcinogens and mutagens. Mutat Res 89:95-136.

*Kundu SK, Bruzek JA, Nair R, et al. 1993. Breath acetone analyzer: Diagnostic tool to monitor dietary fat loss. Clin Chem 39:87-92.

*Kupferschmid LL, Perkins JL. 1986. Organic solvent recycling plant exposure levels. Appl Ind Hyg 1:122-124.

*Ladefoged 0, Perbellini L. 1986. Acetone-induced changes in the toxicokinetics of 2,5-hexanedione in rabbits. Stand J Work Environ Health 122:627-629.

*Ladefoged 0, Hass U, Simonsen L. 1989. Neurophysiological and behavioural effects of combined exposure to 2,5-hexanedione and acetone or ethanol in rats. Pharmacol Toxicol 65:372-375.

*Lagrone FS. 1991. Potential community exposure to toxic chemicals. Environmental Science and Technology 25:366-368.

*Lake RS, Kropko ML. Pezzutti MR, et al. 1978. Chemical induction of unscheduled DNA synthesis in human skin epithelial cell cultures. Cancer Res 38:2091-2098.

*Lam HR, Larsen JJ, Ladefoged 0, et al. 1991. Effects of 2,4-hexanedione alone and in combination with acetone on radial arm maze behavior, the "brain-swelling" reaction and synaptosomal functions. Neurotoxicol Teratol 13:407-412.

*Lamb CB, Jenkins GF. 1952. BOD of synthetic organic chemicals. In: Proceedings of the 8th Industrial Waste Conference, Purdue University. Chelsea MI: Lewis Publishers, Inc., 326-329.

*Landah HD, Herrmann RG. 1950. Retention of vapors and gases in the human nose and lung. Am Med Assoc Arch Ind Health 1:36-45.

*LaRegina J, Bozzelli JW, Harkov R, et al. 1986. Volatile organic compounds at hazardous waste sites and a sanitary landfill in New Jersey. An up-to-date review of the present situation. Environmental Progress 5:18-27.

*Larsen JJ, Lykkegaard M, Ladefoged 0. 1991. Infertility in rats induced by 2,4-hexanedione in combination with acetone. Pharmacol Toxicol 69:43-46.

*Larson TS, Finnegan JK, Haag HD. 1956. Observations on the effect of the edema-producing potency of acids, aldehydes, ketones and alcohols. J Pharmacol Exp Ther 116:119.

*LeBaron FN. 1982. Lipid metabolism 1: Utilization and storage of energy in lipid form. In: Devlin TM, ed. Textbook of biochemistry with clinical correlations. New York, NY: John Wiley & Sons, 464-479, 1243-1265.

*Lee JH, Timmons RB. 1977. Kinetics and mechanism of the gas phase reaction of $O(^3)$ atoms with acetone. Int J Chem Kinet 9: 133-139.

*Lehninger AL. 1970. Biochemistry. New York, NY: Worth Publishers, Inc.

*Leonardos G, Kendall D, Barnard N. 1969. Odor threshold determinations of 53 odorant chemicals, JAPCA 19:91-95.

*Leung HW, Paustenbach DJ. 1988. Application of pharmacokinetics to derive biological exposure indexes from threshold limit values. Am Ind Hyg Assoc J 49:445-450.

*Levey S, Balchum OJ, Medrano V, et al. 1964. Studies of metabolic products in expired air. II. Acetone. J Lab Clin Med 63:574-584.

*Levsen K, Behnert S, Priess B, et al, 1990. Organic compounds in precipitation. Chemosphere 21:1037-1061.

*Levy LJ, Duga J, Girgis M, et al. 1973. Ketoacidosis associated with alcoholism in nondiabetic subjects. Ann Intern Med 78:213-219.

*Lewis GD, Laufman AK, McAnalley BH, et al. 1984. Metabolism of acetone to isopropyl alcohol in rats and humans. J Forensic Sci 29:541-549.

*Lewis SB, Wallin JD, Kane JP, et al. 1977. Effect of diet composition on metabolic adaptations to hypocaloric nutrition: Comparison of high carbohydrate and high fat isocaloric diets. Am J Clin Nutr 30:160-170.

*Lipari F, Dasch JM, Scruggs, WF. 1984. Aldehyde emissions from wood-burning fireplaces. Environmental Science and Technology 18: 326-330.

*Litovitz TL, Holm KC, Bailey KM, et al. 1992. 1991 Annual report of the American Association of Poison Control Centers National Data Collection System. Am J Emerg Med 10:452-505.

*Liu J, Sato C, Marumo F. 1991. Characterization of the acetaminophen-glutathione conjugation reaction by liver microsomes: Species difference in the effects of acetone. Toxicol Lett 56:269-274.

*Lloyd AC. 1978. Trophospheric chemistry of aldehydes. Washington,DC, National Bureau of Standards, 27-48.

*Lo HH, Teets VJ, Yang DJ, et al. 1987. Acetone effects on N-(3,5-dichlorophenyl)succinimideinduced nephrotoxicity. Toxicol Lett 38:161-168.

*Lopez-Soria 0 n FJ, ArgilCs JM. 1985. Simultaneous determination of ketone bodies in biological samples by gas chromatographic headspace analysis. J Chromatogr Sci 23: 120-123.

*Lopez-Soriano, FJ, Alemany M, Argiles JM. 1985. Rat acetoacetic acid decarboxylase inhibition by acetone. Int J Biochem 17:1271-1273.

*Lorr NA, Miller KW, Chung HR, et al. 1984. Potentiation of the hepatotoxicity of nnitrosodimethylamine by fasting, diabetes, acetone and isopropanol. Toxicol Appl Pharmacol 73:423-431.

*Lovegren NV, Fisher GS, Legendre MG, et al. 1979. Volatile constituents of dried legumes. Agric Food Chem 27:851-853.

*Lupulescu AP, Birmingham DJ. 1975. Effect of lipid solvents on protein, DNA, and collagen synthesis in human skin: An electron microscopic autoradiographic study. J Invest Dermatol 65:419- 422.

*Lupulescu AP, Birmingham DJ. 1976. The effect of protective agent against lipid solvent induced damages, ultrastructural and scanning electronmicroscopical study of human epidermis. Arch Environ Health 3 1:33-36.

*Lupulescu AP, Birmingham DJ, Pinkus H. 1973. An electron microscopic study of human epidermis after acetone and kerosene administration. J Invest Dermatol 60:33-45.

*Lupulescu AP, Pinkus H, Birmingham DJ. 1972. Effect of acetone and kerosene on skin ultrastructure. Proceedings-Electron Microscopy Society of America 30:92-93.

*Lyman WJ. 1982. Adsorption coefficient for soils and sediments. In: Handbook of Chemical Property Estimation Methods. New York, NY: McGraw-Hill Book Co., 4-9.

*MacDonald JR, Gandolfi AJ, Sipes IG. 1982a. Acetone potentiation of l,l,Ztrichloroethane hepatotoxicity. Toxicol Lett 13:57-69.

*MacDonald JR, Gandolfi AJ, Sipes IG. 1982b. Covalent binding of “C-l,1,2-trichloroethane to hepatic proteins following acetone pretreatment. Drug Chem Toxicol 5:233-247.

*Mangani F, Ninfali P. 1988. Gas chromatographic determination of acetaldehyde and acetone in human blood by purge and trap, using permeation tubes for calibration. J Chromatogr 437 (1) 294-300.

*Manning DL, Maskarinec MP, Jenkins RA, et al. 1983. High-performance liquid-chromatographic determination of selected gas-phase carbonyls in tobacco smoke. J Assoc Off Anal Chem 66:8-12.

*Marefat P, Shklar G. 1977. Experimental production of lingual leukoplakia and carcinoma. Oral Surg 44:578-586.

*Martinez RD, Buitrago AA, Howell NW, et al. 1992. The near U.V. absorption spectra of several aliphatic aldehydes and ketones at 300 K. Atmos Environ 26A:785-792.

*Mashbitz LM, Sklianskaya RM, Urieva FI. 1936. The relative toxicity of acetone, methylalcohol and their mixtures: II. Their action on white mice. Journal of Industrial Hygiene and Toxicology 18117-122.

*Matsushita T, Goshima E, Miyagaki H, et al. 1969a. [Experimental studies for determining the MAC value of acetone. 2. Biological reaction in the “six-day exposure” to acetone.] Sangyo Igaku 11:507-5 11. (Japanese)

*Matsushita T, Yoshimune A, Inoue T, et al. 1969b. [Experimental studies for determining the MAC value for acetone. 1. Biological reaction in the “one-day exposure” to acetone.] Sangyo Igaku 11:477-484. (Japanese) [Translation in progress]

*Mattheis JP, Fellman JK, Chen PM, et al. 1991. Changes in headspace volatiles during physiological development of Busby Delicious Apples. J Agric Food Chem 39: 1902-1906.

*McCann J, Choi E, Yamasaki E, et al. 1975. Detection of carcinogens as mutagens in the SaZmonelZa/microsome test: Assay of 300 chemicals. Proc Nat1 Acad Sci 72:5135-5139.

*Medinilla J, Espigares M. 1988. Contamination by organic solvents in auto paint shops. Ann Occup Hyg 32:509-513.

*Menck CFM, Cabral-Neto JB, Faljoni-Alario A. 1986. Damages induced in lambda phage DNA by enzyme-generated triplet acetone. Mutat Res 165:9-14.

*Menez JF, Lucas D, Berthou F, et al. 1990. Inhibition by phorbol myristate acetate PMA of cytochrome P-450 induction by acetone [Abstract]. FASEB J 4:A887.

*Menicagli S, Puccini P, Longo V, et al. 1990. Effect of acetone administration on renal, pulmonary and hepatic monooxygenase activities in hamster. Toxicology 64: 141- 153.

*Meyrahn H, Pauly J, Schneider W, et al. 1986. Quantum yields for the photodissociation of acetone in air and an estimate for the life time of acetone in the lower troposphere. J Atmos Chem 4:277- 291.

*Mikalsen A, Alexander J, Andersen RA, et al. 1991. Effect of *in vivo* chromate, acetone and combined treatment on rat liver *in vitro* microsomal chromium(V1) reductive activity and on cytochrome P450 expression. Pharmacol Toxicol 68:456-463.

*Militana LM, Mauch SC. 1989. Statistical modeling of ambient air toxics impact during remedial investigation at a landfill site. In: Super-fund ‘89. Washington,DC, The Hazardous Materials Control Res. Inst., 157-162.

*Mill T, Mabey W. 1985. Photochemical transformations. Environmental Exposure From Chemistry 1:175-216.

*Miller, KW, Yang CS. 1984. Studies on the mechanisms of induction of N-nitrosodimethylamine demethylase by fasting, acetone, and ethanol. Arch Biochem Biophys 229:483-491.

*Mishra NK, Wilson CM, Pant KJ, et al. 1978. Simultaneous determination of cellular mutagenesis and transformation by chemical carcinogens in Fischer rat embryo cells. J Toxicol Environ Health 4:79-91.

*Mohr DH, King CJ. 1985. Identification of polar organic compounds in coal-gasification condensate water by gas chromatography-mass spectrometry analysis of high pressure liquid chromatography fractions. Environmental Science and Technology 19:929-935.

*Moldeus P, Gergely V. 1980. Effect of acetone on the activation of acetaminophen. Toxicol Appl Pharmacol 53:8-13.

*Mender C. 1967. a-Keto aldehyde dehydrogenase, an enzyme that catalyzes the enzymic oxidation of methyglyoxal to pyruvate. J Biol Chem 242:4603-4609.

*Mopper K, Stahovec WL. 1986. Sources and sinks of low molecular weight organic carbonyl compounds in seawater. Marine Chemistry 19:305-321.

*Morgan ET, Koop DE, Coon MJ. 1983. Comparison of six rabbit liver cytochrome P-450 isozymes in formation of a reactive metabolite of acetaminophen. Biochem Biophys Res Commun 112:8-13.

*Mori Y, Yamazaki H, Toyoshi K, et al. 1985. Inhibitory effect of organic solvents on the mutagenicity of N-nitrosodialkylamines in SuZmoneZZu. Mutat Res 142:153-158.

*Morris JB. 1991. Deposition of acetone vapor in the upper respiratory tract of the B6C3Fl mouse. Toxicol Lett 56:187-196.

*Morris JB, Cavanagh DG. 1986. Deposition of ethanol and acetone vapors in the upper respiratory tract of the rat. Fundam Appl Toxicol 6:78-88.

*Morris JB, Cavanagh DG. 1987. Metabolism and deposition of propanol and acetone vapors in the upper respiratory tract of the hamster. Fundam Appl Toxicol 9:34-40.

*Morris JB, Clay RJ, Cavanagh DG. 1986. Species differences in upper respiratory tract deposition of acetone and ethanol vapors. Fundam Appl Toxicol 7:671-680.

*Morris JB, Clay RJ, Trela BA, et al. 1991. Deposition of dibasic esters in the upper respiratory tract of the male and female Sprague-Dawley rat. Toxicol Appl Pharmacol 108:538-546.

*Moshonas MG, Shaw PE. 1990. Flavor evaluation of concentrated aqueous orange essences. J Agric Food Chem 38:2181-4.

*Mourkides GA, Hobbs DC, Koeppe RE. 1959. The metabolism of acetone-2-C14 by intact rats. J Biol Chem 234:27-30.

*NAS. 1976. Vapor-phase organic pollutants: Volatile hydrocarbons and oxidation products. Committee on Medical and Biologic Effects of Environmental Pollutants. National Academy of Sciences, Washington, DC, 23-24, 26-27.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

*NATICH. 1992. National Toxics Information Clearinghouse. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, NC, and State and Territorial Air Pollution Program Administrators/Association of Local Air Pollution Control Officials. May 1992. Online.

*Neiman J, Jones AW, Numminen H, et al. 1987. Combined effect of a small dose of ethanol and 36 hr fasting on blood-glucose response, breath-acetone profiles and platelet function in healthy men. Alcohol Alcohol 22:265-270.

*Nelson DL, Webb BP. 1978. Acetone. In: Grayson M. ed. Kirk-Othmer Encyclopedia of Chemical Technology, vol. 1, 3rd ed. New York, NY: John Wiley and Sons, 179-191.

*Nelson KW, Ege Jr JF, Ross M, et al. 1943. Sensory response to certain industrial solvent vapors. J Ind Hyg Toxicol 25:282-285.

*Nestmann ER, Douglas GR, Kowbel DJ, et al. 1985. Solvent interactions with test compounds and recommendations for testing to avoid artifacts. Environ Mutagen 7:163-170.

*NIOSH. 1978. Criteria for a recommended standard...occupational exposure to ketones. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. DHHS(NIOSH) publication no. 78-173, 5-6.

*NIOSH. 1989. National Occupational Exposure Survey as of 03/22/89. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

*NIOSH. 1990. Manual of Analytical Methods. 3rd ed. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

*NIOSH. 1992. Recommendations for occupational safety and health. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. DHHS (NIOSH) publication no. 92-100.

*Nizyaeva IV. 1982. The hygienic evaluation of acetone. Gig Tr Prof Zabol 6:24-28. (Russian).

*Nomiyama K, Nomiyama H. 1974a. Respiratory retention, uptake and excretion of organic solvents in man. Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. Int Arch Arbeitsmed 32:75-83.

*Nomiyama K, Nomiyama H. 1974b. Respiratory elimination of organic solvents in man: Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. Int Arch Arbeitsmed 32:85-91.

*Norppa H. 1981. The *in vitro* induction of sister chromatid exchanges and chromosome aberrations in human lymphocytes by styrene derivation. Carcinogenesis 2:237-242.

*Norppa H, Heminki K, Sorsa M, et al. 1981. Effect of monosubstituted epoxides on chromosome aberrations and SCE in cultured human lymphocytes. Mutat Res 91:243-250.

*NTP. 1988. National Toxicology Program - report no. PNL-6768. Inhalation developmental toxicology studies: Teratology study of acetone in mice and rats. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institute of Health. NTIS DE89-00567 1.

*NTP. 1991. National Toxicology Program - technical report no. 3. Toxicity studies of acetone in F344/N rats and B6C3F, mice (drinking water studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institute of Health. NIH publication no. 91-3122.

*O'Hara D, Singh HB. 1988. Sensitive gas chromatographic detection of acetaldehyde and acetone using a reduction gas detector. Atmos Environ 22 (11) 2613-2616.

*OSHA. 1989. 29 CFR Part 1910. Air contaminants: Final rule. U.S. Department of Labor, Occupational Safety and Health Administration. Federal Register 54:2923.

*OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment, U.S. Congress. OTA-BA-438, April 1990.

*Otson R, Williams DT, Bothwell PD. 1983. Charcoal-tube technique for simultaneous determination of selected organics in air. Am Ind Hyg Assoc J 44:489-494.

*Ott MG, Skory LK, Holder BB, et al. 1983a. Health evaluation of employees occupationally exposed to methylene chloride: General study design and environmental considerations. Stand J Work Environ Health 9(Supp 1): l-7.

*Ott MG, Skory LK, Holder BB, et al. 1983b. Health evaluation of employees occupationally exposed to methylene chloride: Mortality. Stand J Work Environ Health 9(Supp 1):8-16.

*Ott MG, Skory LK, Holder BB, et al. 1983c. Health evaluation of employees occupationally exposed to methylene: Clinical laboratory evaluation. Stand J Work Environ Health 9(Supp 1):17-25.

*Owen OE, Trapp VE, Skutches CL, et al. 1982. Acetone metabolism during diabetic ketoacidosis. Diabetes 3 1:242-248.

*Palo V, Ilkova H. 1970. Direct gas chromatographic estimation of lower alcohols, acetaldehyde, acetone and diacetyl in milk products. J Chromatogr 53:363-367.

*Pankow D, Hoffmann P. 1989. Dichloromethane metabolism to carbon monoxide can be induced by isoniazid, acetone and fasting. Arch Toxicol Suppl 13:302-303.

*Paterson S, Mackay D. 1989. Correlation of tissue, blood, and air partition coefficients of volatile organic chemicals. Br J Ind Med 46:321-328.

*Paterson P, Sheath J, Taft P, et al. 1967. Maternal and foetal ketone concentrations in plasma and urine. Lancet 11862-865.

*Patten CJ, Ning SM, Lu AYH, et al. 1986. Acetone-inducible cytochrome P-450: Purification, catalytic activity, and interaction with cytochrome b,. Arch Biochem Biophys 251:629-638.

*Peden VH. 1964. Determination of individual semm “ketone bodies,” with normal values in infants and children. J Lab Clin Med 63:332-343.

*Pe’er J, Folberg R, Massicotte SJ, et al. 1992. Clinicopathologic spectrum of primary uveal melanocytic lesions in an animal model. Ophthalmology 99:977-986.

*Peinado J, Lopez-Soriano FJ, Argiles JM. 1986. The metabolism of acetone in the pregnant rat. Biosci Rep 6:983-989.

*Peinado J, Lopez-Soriano FJ, Argiles JM. 1987. Gas chromatographic method for the estimation of acetone and its metabolites in biological samples. J Chromatogr 415:372-376.

*Pellizzari ED, Castillo NP, Willis S, et al. 1979. Identification of organic components in aqueous effluents from energy-related processes. ASTM Spec Tech 686:256-274.

*Pellizzari ED, Hartwell TD, Harris BSH, et al. 1982. Purgeable organic compounds in mother’s milk. Bull Environ Contam Toxicol 28:322-328.

*Perry DL, Chuang CC, Jungclaus GA, et al. 1979. Identification of organic compounds in industrial effluent discharges. Springfield, VA. NTIS PB 294794.

*Pezzagno G, Imbriani M, Ghittori S, et al. 1986. Urinary elimination of acetone in experimental and occupational exposure. Stand J Work Environ Health 12:603-608.

*Phillips M, Greenberg J. 1987. Detection of endogenous acetone in normal human breath, J Chromatogr 422:235-238.

*Phillips M, Greenberg J, Martinez V. 1989. Elevated concentrations of acetone and unidentified compounds in the breath of alcohol abusers. Alcohol Clin Exp Res 13:523-526.

*Pienta RJ. 1980. Transformation of Syrian hamster embryo cells by diverse chemicals and correlation with their reported carcinogenic and mutagenic activities. Chem Mutagen 6:175-202.

Plaa GL. 1988. Experimental evaluation of haloalkanes and liver injury. Fund Appl Toxicol 10:563-570.

*Plaa GL, Traiger GJ. 1972. Mechanism of potentiation of $CC1_4$-induced hepatotoxicity. In: Loomis TA, ed. Pharmacology and the future of man, Vol. 3: Toxicological problems. Basle, Switzerland: Larger, 100-l 13.

*Plaa GL, Hewitt WR, Du Souich P, et al. 1982. Isopropanol and acetone potentiation of carbon tetrachloride-induced hepatotoxicity: Single versus repetitive pretreatments in rats. J Toxico1 Environ Health 9:235-250.

*Plaa GL, Traiger GJ, Hanasono GK, et al. 1973. Effect of alcohols on various forms of chemically induced liver injury. In: Khanna JM, Isreal Y, Kalant H, eds. Alcoholic liver pathology. Proceedings of Alcohol and Drug Research symposium. Toronto, Canada: Drug Addiction Research Foundation, 225244.

*Pomerantz RB. 1950. Acute acetone poisoning from castex. Am J Surg 80:117-118.

*Porter TD, Khani SC, Coon MJ. 1989. Induction and tissue-specific expression of rabbit cytochrome P450IIEl and BE2 genes. Mol Pharmacol 36:61-65.

*Powell FL, Lopez FA, Wagner PD. 1985. Effects of acetone in heparin on the multiple inert gas elimination technique. J Appl Physiol 58(4):1143-l 147.

*Pozzani UC, Weil CS, Carpenter CP. 1959. The toxicological basis of threshold limit values: 5. The experimental inhalation of vapor mixtures by rats, with notes upon the relationship between single dose inhalation and single dose oral data. Industrial Hygiene Journal 20:364-369.

*Price TD, Rittenberg D. 1950. The metabolism of acetone. I. Gross aspects of catabolism and excretion. J Biol Chem 185:449-459.

*Price VF, Jollow DJ. 1983. Mechanism of ketone-induced protection from acetaminophen hepatotoxicity in the rat. Drug Metab Dispos 11:451-457.

*Price KS, Waggy GT, Conway RA. 1974. Brine shrimp bioassay and seawater bod of petrochemicals. J Water Pollut Control Fed 46:63-77.

*Puccini P, Fiorio R, Longo V, et al. 1989. High affinity diethylnitrosamine-deethylase in liver microsomes from acetone-induced rats. Carcinogenesis 10: 1629-1634.

*Puccini P, Fiorio R, Longo V, et al. 1990. Effects of acetone administration on drug-metabolizing enzyme in mice: Presence of a high-affinity diethylnitrosamine de-ethylase. Toxicol Lett 54:143-150.

*Puccini P, Menicagli S, Longo V, et al. 1992. Purification and characterization of an acetone-inducible cytochrome P-450 from hamster liver microsomes. Biochem J 287(Pt. 3):863-870.

*Puntarulo S, Cederbaum AI. 1988. Increased microsomal interaction with iron and oxygen radical generation after chronic acetone treatment. Biochim Biophys Acta 964:46-52.

*Quarles JM, Sega MW, Schenley CK, et al. 1979a. Transformation of hamster fetal cells by nitrosated pesticides in a transplacental assay. Cancer Res 39:4525-4533.

*Quarles JM, Sega MW, Schenley CK, et al. 1979b. Rapid screening for chemical carcinogens: Transforming activity of selected nitroso compounds in a transplacental host-mediated culture system. Nat1 Cancer Inst Monogr 51:257-263.

*Racker E. 1951. The mechanism of action of glyoxalase. J Biol Chem 190:685-696.

*Rahim SA, Bashir WA. 1981. Microdetermination of acetone in aqueous solution. Microchem J 26(3):329-333.

*Rahn RO, Landry LC, Carrier WL. 1974. Formation of chain breaks and thymine dimers in DNA upon photosensitization at 3 13 nm with acetophenone, acetone or benzophenone. Photochem Photobiol 19:75-78.

*Raje RR. 1980. In-vitro toxicity of acetone using coronary perfusion in isolated rabbit heart. Drug Chem Toxicol 3:333-342.

*Raleigh RL, McGee WA. 1972. Effects of short, high-concentration exposures to acetone as determined by observation in the work area. J Occup Med 14:607-610.

*Ramu A, Rosenbaum J, Blaschke TF. 1978. Disposition of acetone following acute acetone intoxication. West J Med 129:429-432.

*Rathbun RE, Tai DY. 1987. Vapor pressures and gas-film coefficients for ketones. Chemosphere 16:69-78.

*Rathbun RE, Shultz DJ, Stephens DW, et al. 1989. Transport and fate of acetone in an outdoor model stream, Stennis Space Center Near Bay St. Louis, Mississippi. U.S. Geological Survey Water-Resources Investigations Report 89-4141.

*Rathbun RE, Stephens DW, Schultz DJ, et al. 1982. Fate of acetone in water. Chemosphere 11:1097-1114.

*Rathbun RE, Stephens DW, Schultz DJ, et al. 1988. Fate of acetone in an outdoor model stream in southern Mississippi. Journal of Hydrology 104:181-209.

*Rathbun RE, Stephens DW, Tai DY. 1991. Fate of acetone in an outdoor model stream with a nitrate supplement, southern Mississippi, U.S.A. Journal of Hydrology 123:225-242.

*Rathbun RE, Stephens DW, Tai DY. 1993. Bacterial degradation of acetone in an outdoor model stream. Environmental Pollution 79: 153- 162.

*Raucy JL, Lasker JM, Lieber CS, et al. 1989. Acetaminophen activation by human liver cytochromes P450IIEl and P450IA2. Arch Biochem Biophys 271:270-283.

*Reichard Jr GA, Haff AC, Skutches CL, et al. 1979. Plasma acetone metabolism in the fasting human. J Clin Invest 63:619-626.

*Reichard Jr GA, Skutches CL, Hoeldtke RD, et al. 1986. Acetone metabolism in humans during diabetic ketoacidosis. Diabetes 35:668-674.

*Rengstorff RH, Khafagy HI. 1985. Cutaneous acetone depresses aqueous humor ascorbate in guinea pigs. Arch Toxicol 5864-66.

*Rengstorff RH, Petrali JP, Sim VM. 1972. Cataracts induced in guinea pigs by acetone, cyclohexanone, and dimethyl sulfoxide. Am J Optom Arch Acad Optom 49:308-319.

*Rengstorff, RH, Petrali JP, Sim VM. 1976. Attempts to induce cataracts in rabbits by cutaneous application of acetone. Am J Optom Physiol Opt 53:41-42.

*Renshaw PK, Mitchell RM. 1956. Acute poisoning following the application of a lightweight cast. British Medical Journal 1:615.

*Rhim JS, Park DK, Weisburger EK, et al. 1974. Evaluation of an *in vitro* assay system for carcinogens based on prior infection of rodent cells with nontransforming RNA tumor virus. J Nat1 Cancer Inst 52:1167-l 173.

*Riddick JA, Bunger WB, Sakano TK. 1986. Techniques of chemistry, Vol. II. Organic Solvents: Physical properties and methods of purification. 4th ed. New York, NY: John Wiley and Sons, Inc., 337-338.

*Roe FJ, Carter RL, Mitchley BC, et al. 1972. On the persistence of tumour initiation and the acceleration of tumour progression in mouse skin tumorigenesis. Int J Cancer 9:264-273.

*Robinson RC, Shorr RGL, Varrichio A, et al. 1989. Human liver cytochrome P-450 related to a rat acetone-inducible, nitrosamine-metabolizing cytochrome P-450: Identification and isolation, Pharmacology 39: 137-144.

*Ronis MJ, Ingelman-Sundberg M. 1989. Acetone-dependent regulation of cytochrome P-450j (IIEl) and P-450b (IIBl) in rat liver. Xenobiotica 19:1161-1165.

*Ronis MJ, Johansson I, Hultenby K, et al. 1991. Acetone-regulated synthesis and degradation of cytochrome P450El and cytochrome P4502Bl in rat liver. J Biochem 198:383-389. [Corrected] [Published erratum appears in Eur J Biochem 200:8 121

*Rooth G. 1967. Insulin action measured by acetone disappearance. Acta Med Stand 182:271-272.

*Rooth G, Carlstrom S. 1970. Therapeutic fasting. Acta Med Stand 187:455-463.

*Rooth G, Gstenson S. 1966. Acetone in alveolar air, and the control of diabetes. Lancet ii:1 102-1105.

*Rosansky SJ. 1982. Isopropyl alcohol poisoning treated with hemodialysis: Kinetics of isopropyl alcohol and acetone removal. J Toxicol Clin Toxicol 19:265-27 1.

*ROSS DJ. 1973. Acute acetone intoxication involving 8 male workers. Ann Occup Hyg 16:73-75.

*Rossman TG, Molina M, Meyer L, et al. 1991. Performance of 133 compounds in the lambda prophage induction endpoint of the microscreen assay and a comparison with S. typhimurium mutagenicity and rodent carcinogenicity assays. Mutat Res 260:349-367.

*Roudabush RL, Terhaar CJ, Fassett DW, et al. 1965. Comparative acute effects of some chemicals on the skin of rabbits and guinea pigs. Toxicol Appl Pharmacol 7:559-565.

*Ruddick JA. 1972. Toxicology, metabolism, and biochemistry of l,2-propanediol. Toxicol Appl Pharmacol 21:102-111.

*Rudney H. 1954. Propanediol phosphate as a possible intermediate in the metabolism of acetone. J Biol Chem 210:361-371.

*Rustung E, Frithjof K, Foyen A. 1931. The uptake and distribution of acetone in the coldblooded organism. Biochem Z 242:366-376.

*Sack RM, Steele DH, Hammerstrom K, et al. 1992. A survey of household products for volatile organic compounds. Atmos Environ 26A:1063-1070.

*Sakai A, Sato M. 1989. Improvement of carcinogen identification in BALB/3T3 cell transformation by application of a 2-stage method. Mutat Res 214:285-296.

*Sakami W, LaFaye JM. 1950. Formation of formate and labile methyl groups from acetone in the intact rat. J Biol Chem 187:369-378.

*Sakami W, LaFaye JM. 1951. The.metabolism of acetone in the intact rat. J Biol Chem 193:199-203.

Sakami W, Rudney H. 1952. The metabolism of acetone and acetoacetate in the mammalian organism. Brookhaven Symp Biol 5: 176- 19 1.

*Sakata M, Kikuchi J, Haga M, et al. 1989. Disposition of acetone, methyl ethyl ketone and cyclohexanone in acute poisoning. J Toxicol Clin Toxicol 27:67-77.

*Sallee ED, Sappington CO. 1949. American Conference of Governmental Industrial Hygienists Eleventh Annual Meeting. American Industrial Hygiene Association Tenth Annual Meeting, April 2-7, 1949, Detroit, MI. Industrial Hygiene Quarterly 10:36-44.

*Sammet D, Lee EW, Kocsis JJ, et al. 1979. Partial hepatectomy reduced both metabolism and toxicity of benzene. J Toxicol Environ Health 5:785-792.

*Sangster J. 1989. Octanol-water partition coefficients of simple organic compounds. Journal of Physical Chemistry Reference Data 18: 1111-1229.

*Sato A, Nakajima T. 1979. Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. Br J Ind Med 36:231-234.

*Sawney BL, Raabe JA. 1986. Ground water contamination: Movement of organic pollutants in the Granby landfill. New Haven, CT: The Connecticut Agricultural Experiment Station Bulletin 833, 9.

*Schaper M, Brost MA. 1991. Respiratory effects of trimellitic anhydride aerosols in mice. Arch Toxicol 65:671-677.

*Schmid BP. 1985. Xenobiotic influences on embryonic differentiation, growth and morphology *in vitro.* Xenobiotica 15:719-726.

*Schnier GG, Laethem CL, Koop DR. 1989. Identification and induction of cytochromes P450, P450IIEl and P450IAl in rabbit bone marrow. J Pharmacol Exp Ther 251:790-796.

*Schrikker ACM, de Vries WR, Zwart A, et al. 1985. Uptake of highly soluble gases in the epithelium of the conducting airways. Pflugers Arch 405:389-394.

*Schrikker ACM, de Vries WR, Zwart A, et al. 1989. The excretion of highly soluble gases by the lung in man. Pflugers Arch 415:214-219.

*Seeber A, Kiesswetter E. 1991. Exposure to mixtures of organic solvents: Subjective symptoms as valid adverse effects? In: Fletcher LD, ed. Proceeding of the 4th International Conference on the Combined Effects of Environmental Factors. 7 l-74.

*Seeber A, Kiesswetter E, Blaszkewicz M. 1992. Correlations between subjective disturbances due to acute exposure to organic solvents and internal dose. NeuroToxicology 13:265-270.

Seegal RF, Bush B, Brosch KO. 1991. Sub-chronic exposure of the adult rat to Aroclor 1254 yields regionally-specific changes in central dopaminergic function. NeuroToxicology 12:55-65.

*Shah JJ, Singh HB. 1988. Distribution of volatile organic chemicals in outdoor and indoor air. Environmental Science and Technology 22: 1381-1388.

*Shahidi F, Rubin L, S'Souza LA. 1986. Meat flavor volatiles: A review of the composition, techniques of analysis, and sensory evaluation. CRC Crit Rev Food Sci Nutr 24:141-243.

*Shepson PB, Hastie DR, Schiff HI, et al. 1991. Atmospheric concentrations and temporal variations of Cl-C3 carbonyl compounds at two rural sites in central Ontario. Atmos Environ 25A:2001-2015.

*Singh HB, Hanst PL. 1981. Peroxyacetyl nitrate (PAN) in unpolluted atmosphere: An important reservoir for nitrogen oxides. Geophys Res Lett 8:941-944.

*Sipes IG, Slocumb ML, Holtzman G. 1978. Stimulation of microsomal dimethyl nitrosamine-ndemethylase by pretreatment of mice with acetone. Chem-Biol Interact 21:155-166.

*Sipes IG, Stripp B, Krishna G, et al. 1973. Enhanced hepatic microsomal activity by pretreatment of rats with acetone or isopropanol. Proc Sot Exp Biol Med 142:237.

*Sippel H, Penttila KE, Lindros KO. 1991. Regioselective induction of liver glutathione transferase by ethanol and acetone. Pharmacol Toxicol 68:391-393.

*Skutches CL, Owen OE, Reichard Jr GA. 1990. Acetone and acetol inhibition of insulin-stimulated glucose oxidation in adipose tissue and isolated adipocytes. Diabetes 39:450-455.

*Smith NB. 1984. Determination of volatile alcohols and acetone in serum by non-polar capillary gas chromatography after direct sample injection. Clin Chem 10:1672-1674.

*Smith R. Fuller DJ, Wedge JH, et al. 1975. Initial effect of injury on ketone bodies and other blood metabolites. Lancet i: 1-3.

*Smyth Jr HF, Carpenter CP, Weil CS, et al. 1962. Range-finding toxicity data: List VI. Am Ind Hyg Assoc J 23:95-107.

*Snider JR, Dawson GA. 1985. Tropospheric light alcohols, carbonyls, and acetonitrile concentrations in the southwestern United States and Henry's law data. J Geophy Res 90:3797-3805.

*Snyder R, Lee EW, Kocsis JJ, et al. 1975. Current concepts of benzene toxicity. CRC Crit Rev Toxicol 3:265-288.

Sollmann T. 1921. Studies of chronic intoxications on albino rats. II. Alcohols (ethyl, methyl and "wood") and acetone. J Pharmacol Exp Ther 16:291-309.

*Song B-J, Gelboin HV, Park S-S, et al. 1986. Complementary DNA and protein sequences of ethanol-inducible rat and human cytochrome P-450s. J Biol Chem 261:16689-16697.

*Song B-J, Veech RL, Park SS, et al. 1989. Induction of rat hepatic N-nitrosodimethylamine demethylase by acetone is due to protein stabilization. J Biol Chem 264:3568-3572.

*Specht H, Miller JW, Valaer PJ. 1939. Acute response of guinea pigs to the inhalation of dimethyl ketone (acetone) vapor in air. Public Health Rep 54:944-954.

*Spencer PS, Bischoff MC, Schaumburg HH. 1978. On the specific molecular configuration of neurotoxic aliphatic hexacarbon compounds causing central-peripheral distal axonopathy. Toxicol Appl Pharmacol 44: 17-28.

*Spicer CW, Riggin RM, Holdren MW, et al. 1985. Atmospheric reaction products from hazardous air pollutant degradation. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA-600/3-85-028.

*SRI. 1991. 1991 Directory of chemical producers. United States of America. Menlo Park, CA: Stanford Research Institute International, 439-440.

*Stafford W, Northrup HJ. 1955. The BOD of textile chemicals. American Dyestuff Reporter 44:355-9.

*Steelman BL, Ecker RM. 1984. Organic contamination of groundwater: An open literature review. Richland, WA: Battelle Pacific Northwest Lab. DE-AC06-76RL0 1830,13.

*Steinberg SM, Kreamer DK. 1993. Evaluation of the sorption of volatile organic compounds by unsaturated calcareous soil from southern Nevada using inverse gas chromatography. Environmental Science and Technology 27:883-888.

*Stewart RD, Hake CL, Wu A, et al. 1975. Acetone: Development of a biologic standard for the industrial worker by breath analysis. Cincinnati, OH: National Institute for Occupational Safety and Health. NTIS PB82-172917.

*Stonebraker RD, Smith Jr AJ. 1980. Containment and treatment of a mixed chemical discharge from “The valley of the drums” near Louisville, Kentucky. In: Proceedings of the Control Hazard Mater Spills National Conference, Nashville, TN, l-10.

*Strange P, Moller A, Ladefoged 0, et al. 1991. Total number and mean cell volume of neocortical neurons in rats exposed to 2,5-hexanedione with and without acetone. Neurotoxicol Teratol 13:401- 406.

*Striegel JA, Carpenter CP. 1961. Progress report for the month ending August 31, 1961. Mellon Institute of Industrial Research. Unpublished study submitted by Union Carbide Corporation, Danbury, CT, to EPA. OTS0536615.

*Strong DF. 1984. Acute acetone poisoning. Can Med Assoc J 51:359-362.

*Stutz DR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradford Communications Corporation, 3 12-3 13.

*Sulway MJ, Malins MJ. 1970. Acetone in diabetic ketoacidosis. Lancet 1:1736-1740.

*Takemoto S, Kuge Y, Nakamoto M. 1981. The measurement of BOD in sea water. Suishitsu Okaku Kenkyu 4:80-90.

*Takeoka GR, Flath RA, Guntert M, et al. 1988. Nectarine volatiles: Vacuum steam distillation versus headspace sampling. J Agric Food Chem 36:553-560.

*Tanii H, Tsuji H, Hashimoto K. 1986. Structure-toxicity relationship of monoketones. Toxicol Lett 30:13-17.

*Tates AD, Kriek E. 1981. Induction of chromosomal aberrations and sister-chromatid exchanges in Chinese hamster cells *in vitro* by some proximate and ultimate carcinogenic arylarnide derivatives. Mutat Res 88:397-410.

*Taylor A, Smith DE, Palmer VJ, et al. 1993. Relationships between acetone, cataracts, and ascorbate in hairless guinea pigs. Ophthalmic Res 25:30-35.

*Teramoto K, Wakitani F, Tanaka H, et al. 1989. Elimination of acetone, 2-propanol, styrene and tetrahydrofuran via exhaled air in rats [Abstract]. J Toxicol Sci 14:325.

*Thorn NS, Agg AR. 1975. The breakdown of synthetic organic compounds in biological processes. Proc R Sot Lond B 189:347-357.

*Thomas RG. 1982. Volatilization from water. In: Handbook of Chemical Property Estimation Methods. New York, NY: McGraw-Hill Book Co, 15-16;15-21.

*Thornalley PJ. 1990. The glyoxalase system: New developments towards functional characterization of a metabolic pathway fundamental to biological life. Biochem J 269: l-l 1.

*Tichenor BA, Mason MA. 1988. Organic emissions from consumer products and building materials to the indoor environment. Japanese Air Pollution Control Association 38:264-268.

*Tindberg N, Ingelman-Sundberg M. 1989. Cytochrome P-450 and oxygen toxicity. Oxygendependent induction of ethanol-inducible cytochrome P-450 (IIEl) in rat liver and lung. Biochemistry 28:4499-4504.

*Tosti A, Bardazzi F, Ghetti P. 1988. Unusual complication of sensitizing therapy for alopecia aneata. Contact Dermatitis 18322.

*Traiger GJ, Plaa GL. 1972. Relationship of alcohol metabolism to the potentiation of CCl_4 hepatotoxicity induced by aliphatic alcohols. J Pharmacol Exp Ther 183:481-488.

*Traiger GJ, Plaa GL. 1973. Effect of aminotriazole on isopropanol- and acetone-induced potentiation of Ccl, hepatotoxicity. Can J Physiol Pharmacol 51:291-296.

*Traiger GJ, Plaa GL. 1974. Chlorinated hydrocarbon toxicity: Potentiation by isopropyl alcohol and acetone. Arch Environ Health 28:276-278.

*TRI90. 1992. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*Trotter MD, Sulway MJ, Trotter E. 1971. The rapid determination of acetone in breath and plasma. Clin Chim Acta 35:137-143.

*Tsukamoto S, Kanegae T, Saito M, et al. 1991. Concentrations of blood and urine ethanol, acetaldehyde, acetate and acetone during experimental hangover in volunteers. Japanese Journal of Alcohol & Drug Dependence 26:550-510.

*Tu YY, Peng R, Chang ZF, et al. 1983. Induction of a high affinity nitrosamine demethylase in rat liver microsomes by acetone and isopropanol. Chem-Biol Interact 44:246-260.

*Uchida Y, Kawa T, Yasugi T, et al. 1990. Personal monitoring sampler for acetone vapor exposure. Bull Environ Contam Toxicol 44:900-904.

*Union Carbide. 1992. Material Safety Data Sheet: Acetone. Solvents & Coatings Materials Division, Union Carbide Chemicals and Plastics Company, Danbury CT.

*Ueng TH, Tsai JN, Ju JM, et al. 1991. Effects of acetone administration of cytochrome P-450-dependent monooxygenases in hamster liver, kidney, and lung. Arch Toxicol 65:45-51.

*Urano K, Kato Z. 1986a. A method to classify biodegradabilities of organic compounds. Journal of Hazardous Material 13: 135-145.

*Urano K, Kato Z. 1986b. Evaluation of biodegradation ranks of priority organic compounds. Journal of Hazardous Material 13:147-159.

*USITC. 1991. Synthetic organic chemicals United States Production and Sales, 1990. USITC Publication 2470, United States International Trade Commission, Washington, DC, 15-5, 15-22, 15-36, 15-38.

*Vainio H, Zitting A. 1978. Interact of styrene and acetone with drug biotransformation enzymes in rat liver. Stand J Work Environ Health 4(Suppl. 2):47-52.

*Vairavamurthy A, Roberts JM, Newman L. 1992. Methods for determination of low molecular weight: Carbonyl compounds in the atmosphere: A review. Atmos Environ 26A: 1965-1993.

*Valentovic M, Ball JG, Anestis D. 1992. Contribution of acetone and osmotic-diuresis by streptozotocin-induced diabetes in attenuation of cephaloridine nephrotoxicity. Toxicology 7 1:245-255.

*Vance DE. 1984. Metabolism of fatty acids and triacylglycerols. In: Zubay G, ed. Biochemistry. Reading, MA:Addison-Wesley Publishing Co., 471-503.

*Van Duuren BL, Loewengart G, Seidman I, et al. 1978. Mouse skin carcinogenicity tests of the flame retardants tris(2,3-dibromopropyl)phosphate, tetrakis(hydroxymethyl)phosphonium chloride, and polyvinyl bromide. Cancer Res 383236-3240.

*Van Duuren BL, Sizak A, Melchiomne S. 1971. Cigarette smoke carcinogenesis - importance of tumor promoters. J Nat1 Cancer Inst 47:235-240.

*Vangala RR, Blaszkewicz M, Bolt HM, et al. 1991. Acute experimental exposures to acetone and ethyl acetate. Arch Toxicol Suppl 14:259-262.

*Van Stekelenburg GJ, Koorevaar G. 1972. Evidence for the existence of mammalian acetoacetate decarboxylase: With special reference to human blood serum. Clin Chim Acta 39:191-199.

*Vasavada HA, Padayatty JD. 1981. Rapid transfection assay for screening mutagens and carcinogens. Mutat Res 91:9-14.

*Walton DC, Kehr EF, Loevenhart AS. 1928. A comparison of the pharmacological action of diacetone alcohol and acetone. J Pharmacol Exp Ther 33: 175-183.

*Ward JM, Quander R, Devor D, et al. 1986. Pathology of aging female SENCAR mice used as controls in skin two-stage carcinogenesis studies. Environ Health Perspect 68:81-89.

*Weiss HS, Pacer KS, Rhoades CA. 1988. Tumor inhibiting effect of pre-promotion with acetone [Abstract]. FASEB 2:4979.

*Weiss HS, O'Connell JF, Hakaim AG, et al. 1986. Inhibitory effect of toluene on tumor promotion in mouse skin. Proc Sot Exp Biol Med 181: 199-204.

*Widmark EMP. 1919. Studies in the concentration of indifferent narcotics in blood and tissues. Acta Med Stand 52:87-164.

*Wigaeus E, Holm S, Astrand I. 1981. Exposure to acetone: Uptake and elimination in man. Stand J Work Environ Health 7:84-94.

*Wigaeus E, Ldf A, Nordgvist M. 1982. Distribution and elimination of 2-[(1)(4)C]-acetone in mice after inhalation exposure. Stand J Work Environ Health 8:121-128.

*Wigaeus E, Löf A, Nordqvist MB. 1984. Uptake, distribution, metabolism, and elimination of styrene in man. A comparison between single exposure and co-exposure with acetone. Br J Ind Med
41539-546.

*Wildenhoff KE. 1972. Diurnal variations in the concentrations of blood acetoacetate, 3-hydroxybutyrate and glucose in normal persons. Acta Med Stand 191:303-306.

*Williamson DH, Whitelaw E. 1978. Physiological aspects of the regulation of ketogenesis. Biochem Sot Symp 43:137-161.

*Yamaguchi T. 1985. Stimulating effects of organic solvents on the mutagenicities of sugardegradation compounds. Agric Biol 49:3363-3368.

*Yanagihara S, Shimada I, Shinoyama E, et al. 1977. Photochemical reactivities of hydrocarbons.
In: Proceedings of the 4th International Clean Air Congress, Tokyo, Japan, 472-477.

*Yoo JSH, Ishizaki H, Yang CS. 1990. Roles of cytochrome-P450IIEl in the dealkylation and denitrosation of N-nitrosodiethylamine in rat liver microsomes. Carcinogenesis VII:2239-2243.

*Yoo J-S, Yang CS. 1985. Enzyme specificity in the metabolic activation of N-nitrosodimethylamine
to a mutagen for Chinese hamster V79 cells. Cancer Res 45:5569-5574.

*Zhou X, Mopper K. 1993. Carbonyl compounds in the lower marine troposphere over the Caribbean
Sea and Bahamas. Journal of Geophysical Research 982385-2392.

*Zimrnermann FK. 1983. Mutagenicity screening with fungal systems. Ann NY Acad Sci 407:186.

*Zimmermann FK, Mayer VW, Scheel I. 1984. Induction of aneuploidy by oncodazole (nocodazole),
an anti-tubulin agent, and acetone. Mutat Res 141:15-18.

*Zimmermann FK, Mayer VW, Scheel I, et al. 1985. Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in *Succharomyces cerevisiue.* Mutat Res 149:339-351.

9. GLOSSARY

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

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

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

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

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

Carcinogen - A chemical capable of inducing cancer.

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

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

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

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

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

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

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

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

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

In Vivo - Occurring within the living organism.

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

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

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

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

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

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

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

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

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

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

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

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

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

q_1*- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The ql* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually ug/L for water, mg/kg/day for food, and ug/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 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

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

RC_{50} - The calculated concentration that decreases the respiratory rate by 50%.

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

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

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

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

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

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

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

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

LEGEND

See LSE Table 2-1

(1). Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

(2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

(3). Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

(4). Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-l).

(5). Species The test species, whether animal or human, are identified in this column.

(6). Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

(7). System This column further defmes the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9). LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

(10). Reference The complete reference citation is given in Chapter 8 of the profile.

(11). CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

(12.) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

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

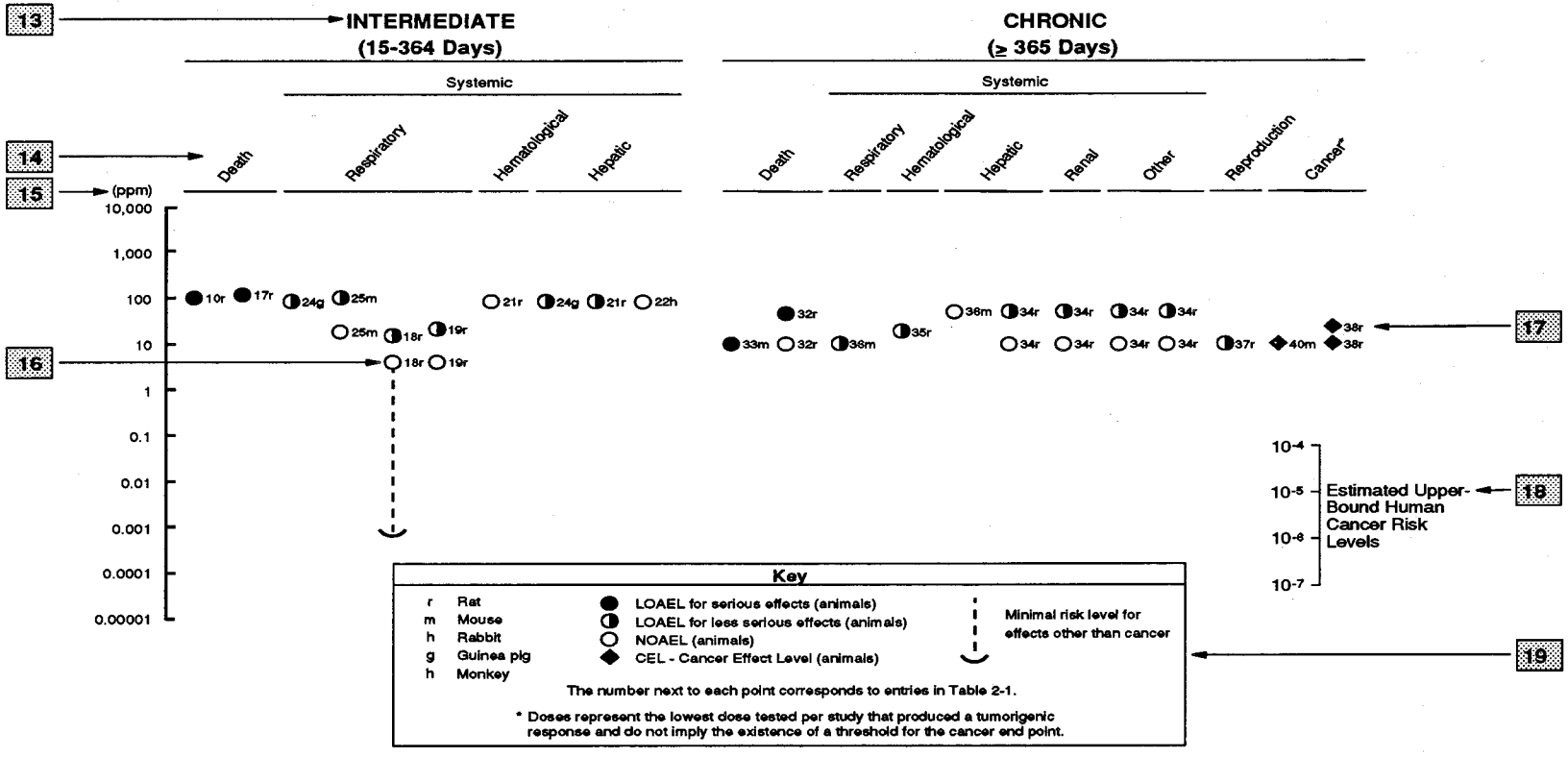
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic							
18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					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

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

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

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

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



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(13). Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14). Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.

(15). Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16). NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17). CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

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

(19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

Chapter 2 (Section 2.4)

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

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

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

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

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

Interpretation of Minimal Risk Levels

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

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

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

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continuous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor of (1, 3, or 10) is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of (1, 3, or 10) are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and (1, 3, or 10) are used for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. Generally an uncertainty factor of 10 is used; however, the MRL Workgroup reserves the right to use uncertainty factors of (1, 3, or 10) based on scientific judgement. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-n-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio

APPENDIX B

STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

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