Toxicological Profile for 2-Hexanone

Draft for Public Comment

April 2018

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

AUTHENTICATED U.S. GOVERNMENT INFORMATION GPO

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UPDATE STATEMENT

A Toxicological Profile for 2-Hexanone was released in 1992. This present edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch
1600 Clifton Road NE
Mailstop F-57
Atlanta, Georgia 30329-4027

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (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 succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is 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.

The focus of the profiles is on health and toxicologic information; therefore, 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 the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance 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; and

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

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov.
Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch

Regular Mailing Address:
1600 Clifton Road, N.E.
Mail Stop F-57
Atlanta, Georgia 30329-4027

Physical Mailing Address:
4770 Buford Highway
Building 102, 1st floor, MS F-57
Chamblee, Georgia 30341

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of 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 EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (e.g., death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Chapter 1	**How Can (Chemical X) Affect Children?**
Chapter 1	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard,

Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. 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 end points.

2. 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.

3. Data Needs Review. The Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

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

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PEER REVIEW

A peer review panel was assembled for 2-hexanone. The panel consisted of the following members:

1. James Blando, Ph.D., School of Community & Environmental Health, Old Dominion University, Norfolk, Virginia;

2. Richard M. LoPachin, Ph.D., Montefiore Medical Center, Bronx, New York;

3. Michael Aschner, Ph.D., Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, New York.

These experts collectively have knowledge of 2-hexanone'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.

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 FOR 2-HEXANONE

This Public Health Statement summarizes the Agency for Toxic Substances and Disease Registry's (ATSDR) findings on 2-hexanone, including chemical characteristics, exposure risks, possible health effects from exposure, and ways to limit exposure.

The U.S. Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are sites targeted for long-term federal clean-up activities. The EPA has found 2-hexanone in at least 224 of the 1,832 current or former NPL sites. The total number of NPL sites evaluated for 2-hexanone is not known. But the possibility remains that as more sites are evaluated, the sites where 2-hexanone is found may increase. This information is important because these future sites may be sources of exposure, and exposure to 2-hexanone may be harmful.

If you are exposed to 2-hexanone, many factors determine whether you'll be harmed. These include how much you are exposed to (dose), how long you are exposed (duration), how often you are exposed (frequency), and how you are exposed (route of exposure). You must also consider the other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

WHAT IS 2-HEXANONE?

2-Hexanone, also known as methyl n-butyl ketone or MBK, is a clear, colorless liquid with a somewhat strong odor. The liquid form can easily evaporate into the air as a vapor. 2-Hexanone was detected in waste waters associated with wood pulping, coal gasification, natural gas, and oil shale operations. 2-Hexanone was formerly used in paint and paint thinner and in various chemical substances. However, since it was found to have harmful health effects, it is no longer made in the United States, and its uses have been restricted. There are no known major natural sources of 2-hexanone in the environment.

More information on the physical and chemical properties and uses of 2-hexanone can be found in Chapters 4 and 5.

WHAT HAPPENS TO 2-HEXANONE WHEN IT ENTERS THE ENVIRONMENT?

When 2-hexanone is released to rivers or lakes, it dissolves very easily, and it may evaporate into the air in a few days. It is expected to have high mobility in soil, so it may seep into groundwater. When

2-hexanone is released to the water, air, or soil, it is probably broken down into smaller products, possibly within a few days.

More information on the releases of 2-hexanone and how it behaves in the environment can be found in Chapter 6.

HOW MIGHT I BE EXPOSED TO 2-HEXANONE?

You can be exposed to 2-hexanone if you live near an industry or hazardous waste site that releases the liquid into groundwater or waste water or the gas form into the surrounding air. These industries include wood pulping mills and oil and gas operations. More information is presented in Chapter 6.

The general population may be exposed to 2-hexanone through ingestion of foods, in which it occurs. 2-Hexanone has been found in foods such as blue cheese, nectarines, nuts, bread, and raw chicken breast. 2-Hexanone has been found in milk and cream at levels up to 0.018 ppm (0.018 parts of 2-hexanone in one million parts of liquid). These levels are far below the levels that have caused harmful effects in animals. It is possible that exposure to small amounts of 2-hexanone may occur through imported products, such as foods, that contain 2-hexanone. It has also been found in drinking water and soil near hazardous waste sites. It has also been detected in air samples near hydraulic fracturing locations. Exposures at these sites may take place if you drink the contaminated water or bathe in it, if you get contaminated soil on your skin, or if you breathe the contaminated air.

More information on how you might be exposed to 2-hexanone is given in Chapter 6.

HOW CAN 2-HEXANONE ENTER AND LEAVE MY BODY?

2-Hexanone can enter your body when you breathe its vapors, eat food, or drink water that contains it, or when you come in contact with it through your skin. About 75% of what is inhaled can pass to the bloodstream through the lungs. If it enters the body by mouth, about 65% of the chemical can pass to the bloodstream through the gastrointestinal tract. It can also pass to the blood through the skin, but the amount that can enter the body this way is not known. In the body, 2-hexanone is distributed to many tissues and organs, including the liver, brain, and kidneys. Most 2-hexanone is transformed mainly in the liver to degradation products (metabolites). Unchanged 2-hexanone and some of its degradation products leave the body in the urine and exhaled air within days regardless of how it entered the body.

More information on how 2-hexanone enters and leaves the body is provided in Chapter 3.

HOW CAN 2-HEXANONE AFFECT MY HEALTH?

The most important health concern for humans from exposure to 2-hexanone is its harmful effects to the nervous system. These effects were seen in workers who were exposed to 2-hexanone for almost a year to concentrations of 2-hexanone that reached up to 36 ppm. The major effects were weakness, numbness, and tingling in the skin of the hands and feet. Similar effects were seen in animals that ate or breathed high levels of 2-hexanone; these effects included weakness, clumsiness, and paralysis. 2,5-Hexanedione, a breakdown product of 2-hexanone causes the adverse effects of 2-hexanone on the nervous system. Based on the limited number of studies of humans exposed to 2-hexanone and on studies of subjects exposed to the industrial chemical, n-hexane, which also produces the breakdown product 2,5-hexanedione, it is evident that the nervous system is a primary target. However, there is no reliable information to determine whether other organs or biological systems in humans could also be targets for 2-hexanone.

It should be mentioned that many of the studies in which the health effects of 2-hexanone in humans or animals were reported did not use pure 2-hexanone. Therefore, we do not know whether the results were caused by 2-hexanone itself or by the other chemicals in the mixture, or whether the other chemicals influenced the toxicity of 2-hexanone.

There are no studies of cancer of 2-hexanone in humans or in animals. The EPA has stated that “there is inadequate information to assess the carcinogenic potential” of 2-hexanone. Neither the Department of Health and Human Services (DHHS) nor the International Agency for Research on Cancer (IARC) have classified 2-hexanone regarding its carcinogenicity.

More information on health effects of 2-hexanone can be found in Chapter 3.

HOW CAN 2-HEXANONE AFFECT CHILDREN?

This section discusses potential health effects of 2-hexanone exposure in humans from when they’re first conceived to 18 years of age.

There are no studies of children exposed to 2-hexanone. However, it is reasonable to assume that, although unlikely, if exposure were to occur, children may experience the same effects on the nervous system observed in adults and in animals.

One study found that exposure of rats to high amounts of 2-hexanone during pregnancy made the offspring more active than those whose mothers had not been exposed to 2-hexanone during pregnancy. However, we cannot predict whether similar effects would occur in humans exposed to 2-hexanone based on results from a single study in animals.

More information on health effects of 2-hexanone in children can be found in Section 3.7.

HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO 2-HEXANONE?

If your doctor finds that you have been exposed to significant amounts of 2-hexanone, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate. You may also contact the state or local health department with health concerns.

To prevent exposure and risk to the general population, the production of 2-hexanone was discontinued in the United States in 1979. Because of these actions and environmental degradation processes, it is likely that neither the general population nor workers are exposed to 2-hexanone in the United States, unless they currently live near an industry or hazardous waste site that release the liquid into waste water or the gas form into the surrounding air. 2-Hexanone is a degradation product of n-hexane, which is a component of fossil fuels, so it is occasionally detected in certain industrial settings. These industries include coal gasification plants, oil shale operations, and wood pulping mills. It is possible that exposure to small amounts of 2-hexanone may occur through imported products containing 2-hexanone, such as foods. Exposure from consumer products manufactured prior to 1982, such as lacquers, primers, sealers, and thinners that contain 2-hexanone is also a possibility. If you find an old product that contains 2-hexanone, you should dispose of it according to the labeled instructions, or contact your local environmental agency or health department to obtain proper disposal information.

ARE THERE MEDICAL TESTS TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 2-HEXANONE?

Tests can be used to find out whether you have recently been exposed to 2-hexanone. The tests measure levels of 2-hexanone or its breakdown products in blood or urine. These tests require special equipment

and are done in a special laboratory, so they are usually not available in a doctor's office. However, these tests cannot be used to predict whether harmful effects will occur. Exposure to some chemicals similar to 2-hexanone produces the same breakdown products that 2-hexanone produces. Therefore, detection of these breakdown products in the blood or urine does not necessarily indicate that you were exposed to 2-hexanone.

More information on how 2-hexanone can be measured in exposed humans is provided in Chapters 3 and 7.

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

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but are not enforceable by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed as “not-to-exceed” levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (e.g., an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

The federal government has set certain regulations and guidelines to help protect people from the possible health effects of 2-hexanone in the workplace. OSHA has set a Permissible Exposure Limit (PEL) of 100 ppm (100 parts of 2-hexanone in 1 million parts of air) as an average exposure level to this chemical in workplace air during an 8-hour work period, over a 40-hour workweek. NIOSH has set a

Recommended Exposure Limit (REL) of 1 ppm of 2-hexanone in work place air as an average exposure during a 10-hour work period for up to a 40-hour workweek. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a 5 ppm Threshold Limit Value (TLV) for 2-hexanone in workplace air as an average during an 8-hour work day.

More information on governmental regulations regarding 2-hexanone can be found in Chapter 8.

WHERE CAN I GET MORE INFORMATION?

If you have any questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below. You may also contact your doctor if experiencing adverse health effects or for medical concerns or questions. ATSDR can also provide publicly available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or

- Write to:
  Agency for Toxic Substances and Disease Registry
  Division of Toxicology and Human Health Sciences
  1600 Clifton Road NE
  Mailstop F-57
  Atlanta, GA 30329-4027

Toxicological profiles and other information are available on ATSDR's web site: http://www.atsdr.cdc.gov.

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO 2-HEXANONE IN THE UNITED STATES

2-Hexanone is a waste product of wood pulping, coal gasification, and *in situ* oil shale operations. 2-Hexanone dissolves very easily in water and can evaporate rapidly into the air as a vapor. Once it is introduced into the environment, 2-hexanone may be degraded by atmospheric photooxidation and direct photolysis or degraded by biodegradation mediated by microorganisms found in most sediment, soils, and water. 2-Hexanone is likely to migrate through the soil and into groundwater since it expected to have very high mobility in soils. Volatilization of 2-hexanone from water surfaces has been observed. A large fraction of vapor-phase 2-hexanone will dissolve in water droplets in the atmosphere, and precipitation may be an important physical removal mechanism. Bioconcentration of this compound in aquatic organisms is not expected to occur.

Significant exposure of the general population to 2-hexanone is not likely at present, as it is no longer manufactured, processed, or used for commercial purposes in the United States. 2-Hexanone was formerly used as a solvent in lacquers and varnish removers, and in various chemical substances. Due to the harmful health effects of this chemical, the lone U.S. producer of 2-hexanone discontinued its production in 1979 and sold its remaining reserves by 1981. However, while 2-hexanone is no longer manufactured or used in the United States, it may be indirectly generated as a waste product during processing at coal gasification plants, *in situ* oil shale operations, and wood pulping mills; therefore, human exposure to 2-hexanone may occur. 2-Hexanone has been detected in drinking water and soil near hazardous waste sites, so the general population living near an industry or hazardous waste site that releases the liquid into waste water or the gas form into the surrounding air has an increased risk of exposure. In the past decade, there has been an increase in oil and natural gas production from shale in the United States; and 2-hexanone has been detected at low levels in air samples near these operations and aqueous samples related to these processes. Exposure to small amounts of 2-hexanone may also occur by ingestion of foods in which it occurs. However, the levels detected in foods are far below the levels that have caused harmful effects in animals. It is possible that exposure to small amounts of 2-hexanone may occur through imported products containing 2-hexanone. Individuals may still be exposed from consumer products manufactured prior to 1982, such as lacquers, primers, sealers, and thinners that contain 2-hexanone.

When 2-hexanone was still being manufactured, occupational exposure may have occurred through inhalation and dermal contact. It is unlikely that many persons are currently occupationally exposed to 2-hexanone, other than as a degradation product resulting from wood pulping, *in situ* oil shale processing, or coal gasification operations.

Children are exposed to 2-hexanone by the same routes that affect adults. Ingestion of foods contaminated with small amounts of 2-hexanone is the most likely route of exposure for children. No data were located regarding 2-hexanone in breast milk; therefore, an adequate determination of the importance of this route of child exposure has not been made.

See Chapter 6 for more detailed information regarding concentrations of 2-hexanone in environmental media.

2.2 SUMMARY OF HEALTH EFFECTS

Limited information is available regarding the effect of 2-hexanone in humans. An early study reported that men exposed to ≥2,300 ppm vapors of a commercial-grade 2-hexanone for brief periods of time (25–60 seconds) found the contaminated air extremely disagreeable due to a strong odor and irritation of the eyes and nasal passages.

Information, from workers in an Ohio fabric finishing plant, indicates that exposure to 2-hexanone affects mainly the nervous system. The study involved the screening of 1,157 employees. The effects consist of a peripheral neuropathy characterized by axon and myelin disruption and axonal swellings involving motor and sensory nerves and resulting in alterations in nerve conduction velocity, ataxia, sensory deficits, and skeletal muscle weakness accompanied by electromyographic abnormalities. Air samples collected at locations in the plant showed that the workers could have been exposed to mean concentrations ranging from 9.2 to 36 ppm 2-hexanone. These exposure levels should be interpreted with caution since there was also exposure to other chemicals and there may have been significant oral and dermal exposure to solvents due to practices such as eating on/in work areas or washing the hands in solvent. Exposure to 2-hexanone was presumably responsible for adverse neurological effects in a furniture finisher and in three painters. No exposure data were available in these cases, plus the subjects had also been exposed to other chemicals.

2. RELEVANCE TO PUBLIC HEALTH

Studies have shown that 2,5-hexanedione, a metabolite of 2-hexanone, is the toxicologically active chemical responsible for the neurotoxic effects of 2-hexanone. 2,5-Hexanedione is also a metabolite of *n*-hexane, a chemical with extensive industrial use, so considerably more information regarding effects of exposure to 2,5-hexanedione in humans can be found in documents regarding *n*-hexane.

Aside from the neurotoxic effects, there was little evidence of adverse effects in the affected workers at the Ohio plant. Results of clinical tests used to assess liver and kidney function, as well as results of hematological assessments, were within normal ranges. Body weight was reduced in some workers found to have moderate to severe neurological impairment. However, there was no information regarding the subject's appetite and/or actual food consumption. The study stated that the workers regained weight when the use of 2-hexanone was discontinued.

Exposure of most animal species to 2-hexanone by any route of exposure results in neurotoxic effects similar to those reported in humans. Comparative studies also have shown the relative species sensitivity to 2-hexanone as chicken > cat > dog > primate > rat. Involvement of the central nervous system has also been reported in studies in animals; detailed studies regarding central nervous system involvement have been conducted in animals exposed directly to 2,5-hexanedione. The lowest lowest-observed-adverse-effect level (LOAEL) for neurotoxicity in an inhalation study with 2-hexanone was 50 ppm in rats and hens exposed intermittently for several months. It should be noted, however, that the purity of the 2-hexanone used in the rat study was not reported and, in the study in hens, the test material was 70% 2-hexanone and 30% methyl isobutyl ketone (MiBK). This is important because MiBK has been reported to induce total cytochrome P-450 in the liver, thus potentially increasing the formation of 2,5-hexanedione, the neurotoxic metabolite of 2-hexanone.

Limited systemic toxicity of 2-hexanone was reported in inhalation and oral studies in animals. It should be mentioned that many studies tested only one concentration/dose of 2-hexanone, so no information on dose-response was provided. In addition, very few studies stated the purity of the 2-hexanone tested, so there is uncertainty regarding whether the reported effects were caused by 2-hexanone or by the interactive action of 2-hexanone with other chemicals, possibly MiBK.

2-Hexanone induced skeletal muscle pathology of neurogenic origin in rats following repeated inhalation (≥330 ppm) or oral exposure (≥480 mg/kg/day). Alterations generally consisted of atrophy and degenerative changes. Exposure to 2-hexanone also resulted in decreased weight gain in inhalation

studies (≥700 ppm) in rats and monkeys and in oral studies in rats (≥266 mg/kg/day). However, without data on food consumption in most of these studies, the usefulness of this information is limited.

2-Hexanone did not induce histological alterations in lymphoreticular organs or tissues of rats or cats in long-term inhalation or oral studies. However, none of these studies examined parameters of immunocompetence, so no firm conclusions regarding immunotoxicity of 2-hexanone can be made.

The evaluation of potential reproductive toxicity of 2-hexanone yielded mixed results. Exposure to 700 ppm pure 2-hexanone for 11 weeks reduced testes weight and induced atrophy of the testicular germinal epithelium of male rats, whereas chronic exposure of male rats and female cats to ≤330 ppm 2-hexanone of unreported purity did not induce microscopic alterations in the reproductive organs of either species. In oral studies, 2-hexanone induced testicular toxicity in male rats when given by gavage but not when given in the drinking water to male rats in comparable doses. Fertility was not tested in any of these studies. It seems that a 2-generation reproductive study could provide useful data.

There are not enough data to determine whether 2-hexanone is a developmental toxicant. In the only developmental study available, exposure of rats to ≥1,000 ppm 2-hexanone (unknown purity) during gestation resulted in reduced maternal weight during gestation, reduced birth weight, reduced pups per litter, and behavioral alterations in the offspring tested at various times between weaning and the geriatric stage. The investigators concluded that the results suggested that exposure to 2-hexanone may be associated with hyperactivity in the young and subsequent decreased activity in older animals; however, definite conclusions could not be drawn.

There are no studies of cancer from exposure to 2-hexanone in humans or in animals. The EPA has stated that “there is inadequate information to assess the carcinogenic potential” of 2-hexanone. Neither the Department of Health and Human Services (DHHS) nor the International Agency for Research on Cancer (IARC) have classified 2-hexanone regarding its carcinogenicity.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been established for 2-hexanone. 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 1990), 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.

Inhalation MRLs

An acute-duration inhalation MRL for 2-hexanone was not derived due to lack of appropriate studies in humans or in animals. The only information located regarding effects in humans is that men (unknown number) exposed to ≥2,300 ppm vapors of a commercial-grade 2-hexanone for brief periods of time (25–60) seconds found the contaminated air extremely disagreeable due to a strong odor and irritation of the eyes and nasal passages (Schrenk et al. 1936). The same group of investigators reported that an unspecified number of guinea pigs exposed to 2,300 ppm 2-hexanone showed signs of eye and nose irritation after 1 minute of exposure and lacrimation after 10 minutes of exposure; no such signs were reported in guinea pigs exposed to 1,000 ppm 2-hexanone. Exposure to 6,500 ppm for 540 minutes caused lethality. This information is insufficient for MRL derivation.

An intermediate-duration inhalation MRL for 2-hexanone was not derived due to inadequacies of the human database and the fact that the lowest LOAELs in animal studies were classified as serious LOAELs, and ATSDR does not derive MRLs based on serious LOAELs (Chou et al. 1998). Pertinent human data are available from a study of workers at a coated fabric plant (Allen et al. 1975; Billmaier et al. 1974). Eighty-six cases of distal polyneuropathy were reported among 1,157 workers exposed to 2-hexanone and other chemicals. The time worked in the print department by persons with peripheral neuropathy ranged from 5 weeks to 27 years. The mean concentration of 2-hexanone in an area where operators spent 60–80% of their time was 9.2 ppm. However, this exposure level is not a reliable LOAEL for the following several reasons. In that same working area, the mean concentration of methyl ethyl

ketone (MEK) was 331 ppm, and MEK has been shown to potentiate the effects induced by 2,5-hexanedione, the toxic metabolite of 2-hexanone (Saida et al. 1976; Yu et al. 2002). In addition, workers reportedly exhibited poor work practices, such as eating in work areas, washing hands with solvent, and using solvent-soaked rags to clean equipment and machinery. It was also noted that no respirators were worn, and gloves were rarely used. All of these issues may have contributed to considerable oral and dermal exposure to 2-hexanone. Results of clinical tests used to assess liver and kidney function, as well as results of hematological assessments, were within normal ranges. Body weight was reduced in some workers found to have moderate to severe neurological impairment. Because of serious confounders, this study is not appropriate for MRL derivation.

There are several intermediate-duration studies in animals that identified the nervous system as the target for 2-hexanone. Species examined include rats, monkeys, cats, and hens. While hens have proved to be a good, sensitive model for 2-hexanone-induced neuropathy and studies in this species are useful for hazard identification, they are not useful for risk assessment. Because the digestive and respiratory systems are different from mammals, it is not known whether the dose-response in hens is applicable to humans.

Additional limitations of the animal database include the fact that several of the studies available tested only one exposure concentration, thus not allowing the construction of dose-response relationships, and not providing information regarding the purity of the 2-hexanone tested. As previously mentioned, knowing the purity of the 2-hexanone tested is important because commercial grades of 2-hexanone may vary in purity from 70 to 96% and up to 30% may be MiBK (Topping et al. 2001). MiBK has been shown to potentiate the neurotoxicity of ketogenic chemicals such as *n*-hexane by inducing microsomal cytochrome P-450 content in liver, resulting in increased production of the *n*-hexane and the 2-hexanone active metabolite, 2,5-hexanedione (Abou-Donia et al. 1985c, 1991; Lapadula et al. 1991).

While the limitations mentioned above do not totally preclude derivation of an intermediate-duration inhalation MRL for 2-hexanone, such an MRL would carry low confidence. However, the main reason for not deriving an intermediate-duration inhalation MRL for 2-hexanone is that the lowest exposure concentrations tested induced serious neurological effects in rats that were classified as serious LOAELs. For example, Duckett et al. (1979) reported the lowest LOAEL at 50 ppm (only exposure concentration tested) for wide spread demyelination of the sciatic nerve in 32 out of 40 rats exposed intermittently to 2-hexanone for 6 months. In another study, exposure of rats almost continuously to 100 ppm pure 2-hexanone caused peripheral and central nervous system histopathology (Egan et al. 1980). The exposure regime did not induce clinical signs during the first 4 months of the study; however, alterations

in the peripheral and central nervous system became evident around this time. Changes consisted of axonal swelling and secondary demyelination in axons from peripheral nerves and axonal swelling in the medulla oblongata and cerebellum in the central nervous system. By 6 months, changes became more severe; nerve fiber damage by 6 months was described by the investigators as "*strikingly advanced.*" Therefore, the 100 ppm exposure level in the Egan et al. (1980) study represents a serious LOAEL. It is very likely that if exposure had continued, degeneration would have kept progressing and clinical signs would have been apparent.

In another intermediate-duration inhalation study, rats were exposed intermittently to 100 ppm (lowest levels tested) of a commercial-grade 2-hexanone for 29 weeks (Johnson et al. 1977). Measurements of sciatic-tibial nerve conduction velocity on week 28 showed a 45% decrease in conduction velocity compared to measurements performed on week 24 (from 45 to 22 m/second), making the 100 ppm exposure level a serious LOAEL. In the same study, exposure of monkeys to 100 ppm 2-hexanone for 41 weeks induced a significant decrease in sciatic-tibial nerve conduction velocity (about 12%) compared to controls, although data presented in a figure seemed to show that a significant reduction relative to controls already occurred after 4 months of exposure. Monkeys exposed to 330 ppm 2-hexanone showed a progressive decrease in motor conduction velocity relative to controls beginning at 3 months of exposure. In this group, after 6 months, mean conduction velocity was 63% of the mean measured in controls. No histological examinations of nervous system tissues were performed in this study. Other intermediate-duration inhalation studies in rats and cats showed severe neuropathy occurring at exposure levels ≥225 ppm 2-hexanone (Katz et al. 1980; Mendell et al. 1974b; Saida et al. 1976; Spencer et al. 1975). In conclusion, an intermediate-duration inhalation MRL for 2-hexanone was not derived because the lowest exposure levels tested, 50 ppm in Duckett et al. (1979) and 100 ppm in Egan et al. (1980) and Johnson et al. (1977), caused neurological effects in rats that were classified as serious LOAELs.

A chronic-duration inhalation MRL for 2-hexanone was not derived due to lack of adequate data. An occupational study reported that some workers exposed to 2-hexanone developed peripheral neuropathy (Allen et al. 1975; Billmaier et al. 1974). However, as summarized above, confounders such as exposures to other chemicals, as well as likely multi-route exposure, preclude using this study for MRL derivation.

Two chronic-duration inhalation studies have been conducted, one in rats exposed intermittently to 2-hexanone for 72 weeks (Krasavage and O'Donoghue 1977) and one in cats similarly exposed for 2 years (O'Donoghue and Krasavage 1979). In both studies, the animals were exposed to 0, 100, or 330 ppm 2-hexanone of unknown purity. In rats, exposure to 330 ppm 2-hexanone induced equivocal

signs of neuropathy as stated by the investigators based on manifestation of clinical signs and histopathological examinations of peripheral and central neural tissues. However, poor reporting of the results made it difficult to define a no-observed-adverse-effect level (NOAEL) and LOAEL. Specifically, in some cases, the control and low-exposure groups may have been combined, which made it difficult to ascertain whether effects were treatment-related. In cats, exposure to 330 ppm 2-hexanone induced axonal degeneration in the peripheral and central nervous system below the level of the cerebellum and pons; cats in the 100 ppm exposure group were not affected. Even if the 100 ppm exposure level were considered a NOAEL for neurological effects in rats and cats in these chronic-duration studies, a chronic-duration inhalation MRL could not be derived because severe neurological effects were reported in rats exposed to 100 ppm 2-hexanone in two intermediate-duration studies (Egan et al. 1980; Johnson et al. 1977) and in rats exposed to an even lower concentration of 50 ppm 2-hexanone in another intermediate-duration study (Duckett et al. 1979).

Oral MRLs

An acute-duration oral MRL was not derived for 2-hexanone because of an insufficient database. There are no human data and the database in animals consists of a report of an oral LD_{50} in rats (Smyth et al. 1954) and a study of the potentiation action of 2-hexanone on liver and kidney toxicity caused by chloroform (Brown and Hewitt 1984). In that study, a single high dose of 1,500 mg pure 2-hexanone/kg alone (only dose tested) did not induce morphological alterations in the liver, but produced epithelial degeneration in proximal tubules of the kidneys. This information is insufficient for MRL derivation.

An intermediate-duration oral MRL for 2-hexanone was not derived due to lack of relevant data in humans and the fact that the lowest dose tested in an animal study induced serious neurological effects in guinea pigs that were classified as serious LOAELs, and ATSDR does not derive MRLs based on serious LOAELs (Chou et al. 1998). There are several animal studies that identified the nervous system as the target for 2-hexanone. For example, Abdel-Rahman et al. (1978) reported an approximately 40% reduction in locomotor activity in guinea pigs dosed with approximately 310 mg 2-hexanone/kg/day in the drinking water for 24 weeks, pupillary responses to light stimuli were also significantly reduced at this dose level. No information was provided regarding results obtained with a lower dose of approximately 124 mg/kg/day. Union Carbide (1977) reported peripheral neuropathy in rats dosed with ≥480 mg 2-hexanone/kg/day in the drinking water for 120 days. Eben et al. (1979) reported hindlimb weakness in rats dosed by gavage with 400 mg 2-hexanone/kg/day (only dose tested) for 40 weeks; no histological examinations were conducted in this study. Krasavage et al. (1980) reported clinical signs and

microscopic evidence of neuropathy in rats dosed by gavage with 660 mg 2-hexanone/kg/day (only dose tested) for 90 days. In both Eben et al. (1979) and Krasavage et al. (1980), the true LOAEL was probably lower than the doses tested. Because the lowest dose tested for which there is information on induced effects (310 mg/kg/day) is considered a serious LOAEL, an intermediate-duration oral MRL was not derived for 2-hexanone.

- A provisional MRL of 0.05 mg/kg/day has been derived for chronic-duration oral exposure (365 days or longer) to 2-hexanone.

The MRL is based on adverse neurological effects in male Sprague-Dawley rats exposed to 2-hexanone in the drinking water for 13 months (O'Donoghue et al. 1978). No human studies were located and the only relevant information in animals is that from the study by O'Donoghue et al. (1978). In that study, male Sprague-Dawley rats exposed to ≥143 mg 2-hexanone/kg/day (96.1% pure) in the drinking water developed peripheral neuropathy; the first clinical signs appearing in rats dosed with 560 mg 2-hexanone/kg/day, the highest dose tested. At termination, histological examination of neural tissues showed that rats from all treated groups (143, 266, and 560 mg/kg/day) had "giant" axonal neuropathy. Neurogenic skeletal muscle atrophy in proximal and distal hindlimb musculature was also evident. Relevant incidence data are shown in Table 2-1. A more detailed summary of O'Donoghue et al. (1978) study is presented in Appendix A.

Inspection of Table 2-1 shows that the most sensitive neural tissues for developing axonal swellings were the spinal cord and peripheral nerve. Of these two data sets, the incidence of axonal swelling in peripheral nerve is preferred for MRL derivation because 10 rats were included for analysis in the three treated groups and in the control group, as opposed to the data set for the lesion in the spinal cord. It should be noted that atrophy of the muscle fibers is a phenomenon secondary to damage to the innervating axons, reflecting "Wallerian-type" degeneration.

Benchmark dose (BMD) modelling of the incidence data for axonal swelling in peripheral nerve of rats in the O'Donoghue et al. (1978) study was considered, but was rejected because a nearly maximum response level (80%) was reached with the lowest dose tested. In such cases, there is great uncertainty because the BMD may be just below the first dose or orders of magnitude lower (EPA 2012a). Therefore, the NOAEL/LOAEL approach was used for MRL derivation. Applying a combined uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 for human variability) and a modifying factor of 3 (to account for an 80% response rate at the lowest dose) to the LOAEL of 143 mg/kg/day results in a chronic-duration oral provisional MRL of 0.05 mg/kg/day for 2-hexanone.

Table 2-1. Incidence Data for Neuropathological Lesions in Rats Exposed to 2-Hexanone for 13 Months

	Axonal swelling				Myofibrillar atrophy	
Dose (mg/kg/day)	Brain	Spinal cord	Dorsal root ganglia	Peripheral nerve	Quadriceps muscle	Calf muscle
0	0/10	0/5	0/5	0/10	0/10	0/10
143	2/10	7/10[a]	0/7	8/10[a]	1/10	2/10
266	4/10[a]	5/5[a]	0/5	10/10[a]	5/10[a]	6/10[a]
560	8/10[a]	5/5[a]	3/5	10/10[a]	10/10[a]	10/10[a]

[a]p<0.05 per Fisher Exact Test conducted by SRC, Inc.

Source: O'Donoghue et al. 1978

3. HEALTH EFFECTS

3.1 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 on the toxicology of 2-hexanone. 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.

3.2 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 (e.g., death, systemic, immunological, neurological, reproductive, developmental, 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. LOAELs 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.

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

3.2.1 Inhalation Exposure

Numerous studies have been conducted in which animals were exposed to 2-hexanone via inhalation. However, the purpose of many of these studies was to assess the potential effects of combined exposure to 2-hexanone and another substance (usually chloroform or MEK). Study design has consequently involved exposure to only one concentration of 2-hexanone as a control exposure. A single high concentration of 2-hexanone was used in several other studies in order to elicit and study histopathological changes in the affected nervous tissue. In addition, the grade or purity of the 2-hexanone used was not stated in many studies, or in some cases, 2-hexanone with purity as low as 70% was used. As a result of these various complications, the usefulness of some of the available data is limited.

3.2.1.1 Death

No studies were located regarding death in humans following inhalation exposure to 2-hexanone. Death occurred in guinea pigs following exposure to 6,500 ppm of commercial-grade 2-hexanone for 540 minutes or to 20,000 ppm for 70 minutes (Schrenk et al. 1936). Death was preceded by incoordination, narcosis, and gasping-type respiration. The exposure concentration of 6,500 ppm is presented as a lethal exposure level in Table 3-1 and in Figure 3-1.

Table 3-1 Levels of Significant Exposure to 2-Hexanone - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Gn Pig (NS)	810 min				6500 (death in 540 minutes)	Schrenk et al. 1936 UNKNOWN	
Neurological								
2	Gn Pig (NS)	810 min		1000	2300 (incoordination after 90 minutes of exposure)		Schrenk et al. 1936 UNKNOWN	
INTERMEDIATE EXPOSURE								
Systemic								
3	Monkey	25-41 wk 5 d/wk 6 hr/d	Bd Wt	100 M			Johnson et al. 1977 UNKNOWN	
4	Rat	6 mo 5 d/wk 8 hr/d	Hepatic	50			Duckett et al. 1979 UNKNOWN	
			Renal	50				
5	Rat	6 mo 7 d/wk 22 hr/d	Bd Wt	100 M			Egan et al. 1980 PURE	
6	Rat	25-29 wk 5 d/wk 6 hr/d	Bd Wt	100 M	1000 M (decreased body weight)		Johnson et al. 1977 UNKNOWN	
7	Rat	11 wk 72 hr/wk 18 hr/d	Hemato			700 M (40% decrease in WBCs)	Katz et al. 1980 PURE	
			Bd Wt		700 M (decreased weight gain)			

Table 3-1 Levels of Significant Exposure to 2-Hexanone - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Neurological								
8	Monkey	41 wk 5 d/wk 6 hr/d			100 M (12% reduced nerve conduction velocity)	1000 M (36% reduction in motor nerve conduction velocity)	Johnson et al. 1977 UNKNOWN	
9	Rat (Wistar)	6 mo 5 d/wk 8 hr/d				50 (sciatic nerve demyelination in 32/40 rats)	Duckett et al. 1979 UNKNOWN	
10	Rat (Sprague-Dawley)	6 mo 7 d/wk 22 hr/d				100 M (peripheral and central histopathology)	Egan et al. 1980 PURE	
11	Rat	29 wk 5 d/wk 6 hr/d				100 M (45% reduced nerve conduction velocity)	Johnson et al. 1977 UNKNOWN	
12	Rat (Sprague-Dawley)	11 wk 72 hr/wk 18 hr/d				700 M (severe neuropathy)	Katz et al. 1980 PURE	
13	Rat	12 wk 24 hr/d 7 d/wk				400 (neuropathy)	Mendell et al. 1974 UNKNOWN	
14	Rat	6-9.5 wk 24 hr/d				225 (paralysis, histopathology)	Saida et al. 1976 UNKNOWN	

Table 3-1 Levels of Significant Exposure to 2-Hexanone - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
15	Rat	4 mo 5 d/wk 6 hr/d				1300 (nerve degeneration)	Spencer et al. 1975 UNKNOWN	
16	Cat	>8 wk 24 hr/d 7 d/wk				400 F (neuropathy, histopathology)	Mendell et al. 1974 UNKNOWN	
Reproductive								
17	Rat	11 wk 72 hr/wk 18 hr/d				700 M (decreased testes weight, histopathology)	Katz et al. 1980 PURE	
Developmental								
18	Rat	21 Gd 6 hr/d				1000 F (behavioral effects in offspring)	Peters et al. 1981 UNKNOWN	

Table 3-1 Levels of Significant Exposure to 2-Hexanone - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
19	Rat (Sprague-Dawley)	72 wk 5 d/wk 6 hr/day	Resp	330 M			Krasavage and O' Donoghue 1977 UNKNOWN	NOAELs are for tissues histopathology.
			Cardio	330 M				
			Gastro	330 M				
			Hemato	330 M				
			Musc/skel	100 M		330 M (degenerative changes in skeletal muscle fibers)		
			Hepatic	330 M				
			Renal	330 M				
			Endocr	330 M				
			Ocular	330 M				
			Bd Wt	330 M				

Table 3-1 Levels of Significant Exposure to 2-Hexanone - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
20	Cat Domestic	2 yr 7 d/wk 6 hr/d	Resp	330 F			O'Donoghue and Krasavage 1979 UNKNOWN	
			Cardio	330 F				
			Gastro	330 F				
			Hemato	330 F				
			Musc/skel	330 F				
			Hepatic	330 F				
			Renal	330 F				
			Endocr	330 F				
			Ocular	330 F				
			Bd Wt	330 F				
			Metab	330 F				
Immuno/ Lymphoret								
21	Rat (Sprague-Dawley)	72 wk 5 d/wk 6 hr/day		330 M			Krasavage and O' Donoghue 1977 UNKNOWN	NOAEL is for histopathology.of the spleen and lymph nodes.
22	Cat Domestic	2 yr 7 d/wk 6 hr/d		330 F			O'Donoghue and Krasavage 1979 UNKNOWN	NOAEL is for spleen, thymus, and lymph nodes histopathology.
Neurological								
23	Rat (Sprague-Dawley)	72 wk 5 d/wk 6 hr/day		100 M		330 M (peripheral neuropathy)	Krasavage and O' Donoghue 1977 UNKNOWN	

Table 3-1 Levels of Significant Exposure to 2-Hexanone - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
24	Cat Domestic	2 yr 7 d/wk 6 hr/d		100 F		330 F (axonal degeneration in central and peripheral nervous system)	O'Donoghue and Krasavage 1979 UNKNOWN	
Reproductive								
25	Rat (Sprague-Dawley)	72 wk 5 d/wk 6 hr/day		330 M			Krasavage and O' Donoghue 1977 UNKNOWN	NOAEL is for histopathology.of the testes.
26	Cat Domestic	2 yr 7 d/wk 6 hr/d		330 F			O'Donoghue and Krasavage 1979 UNKNOWN	NOAEL is for reproductive organs histopathology.

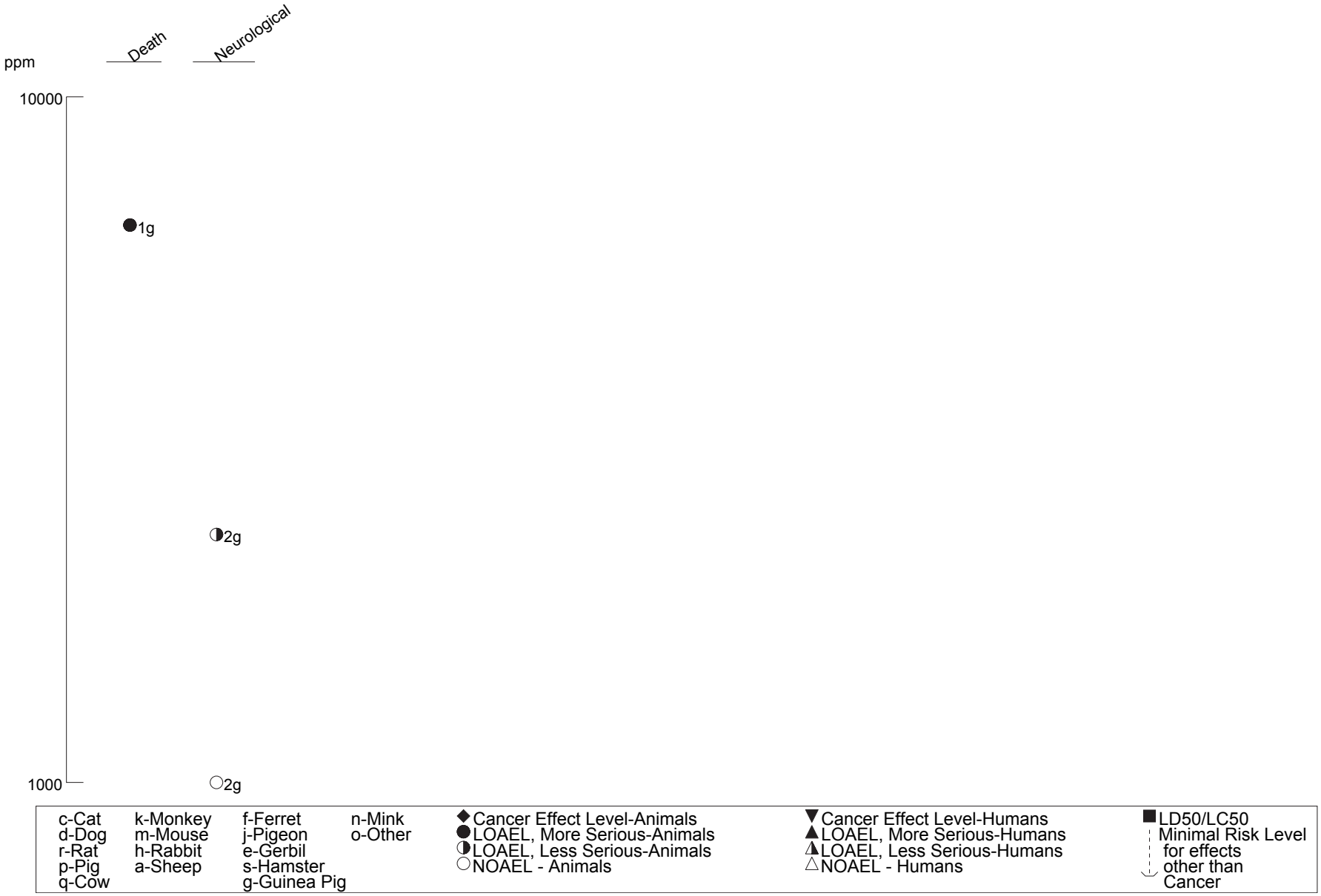
a The number corresponds to entries in Figure 3-1.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Gd = gestational day; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolism; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); yr = year(s)

3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to 2-Hexanone - Inhalation

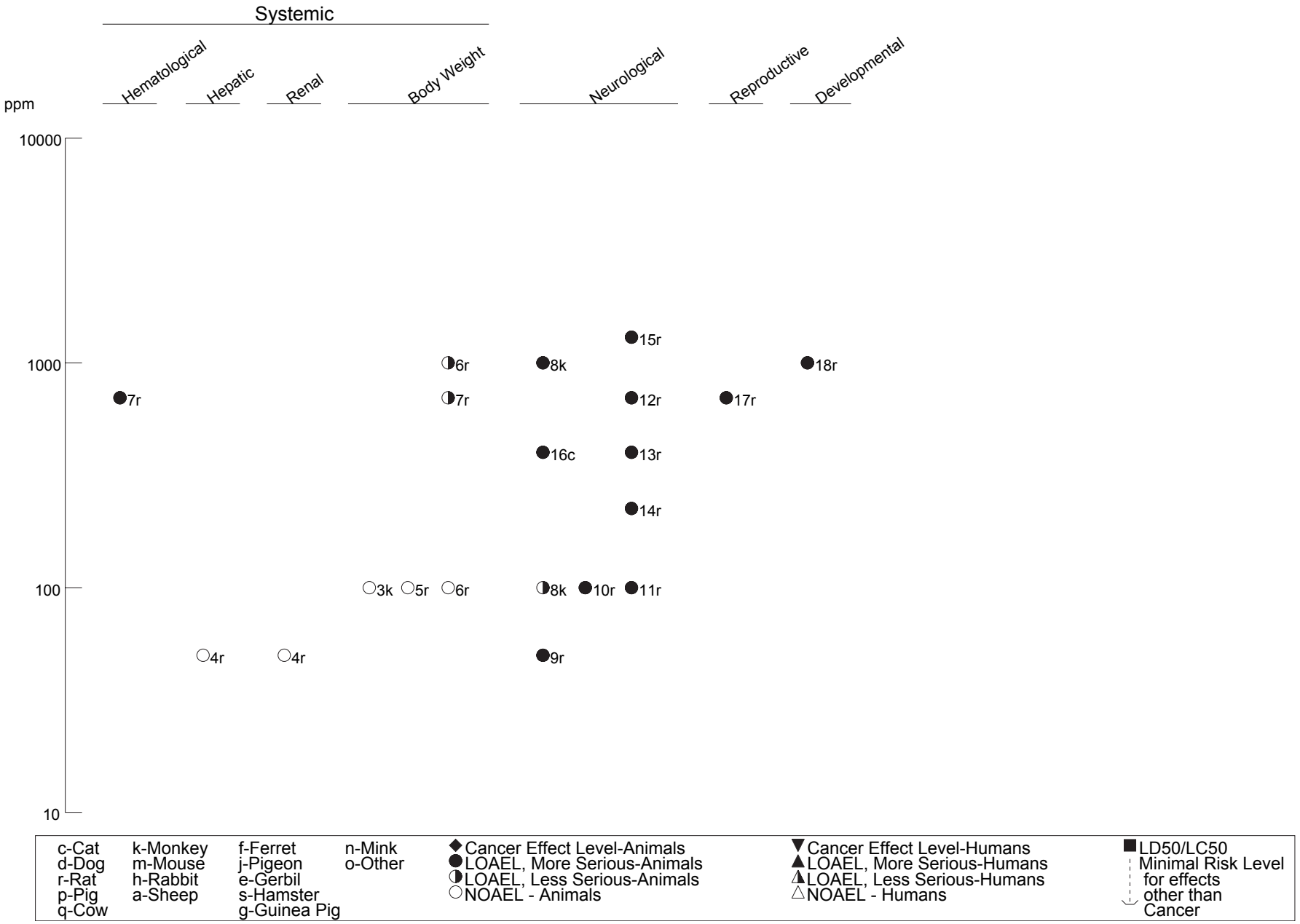
Acute (≤14 days)



3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to 2-Hexanone - Inhalation *(Continued)*

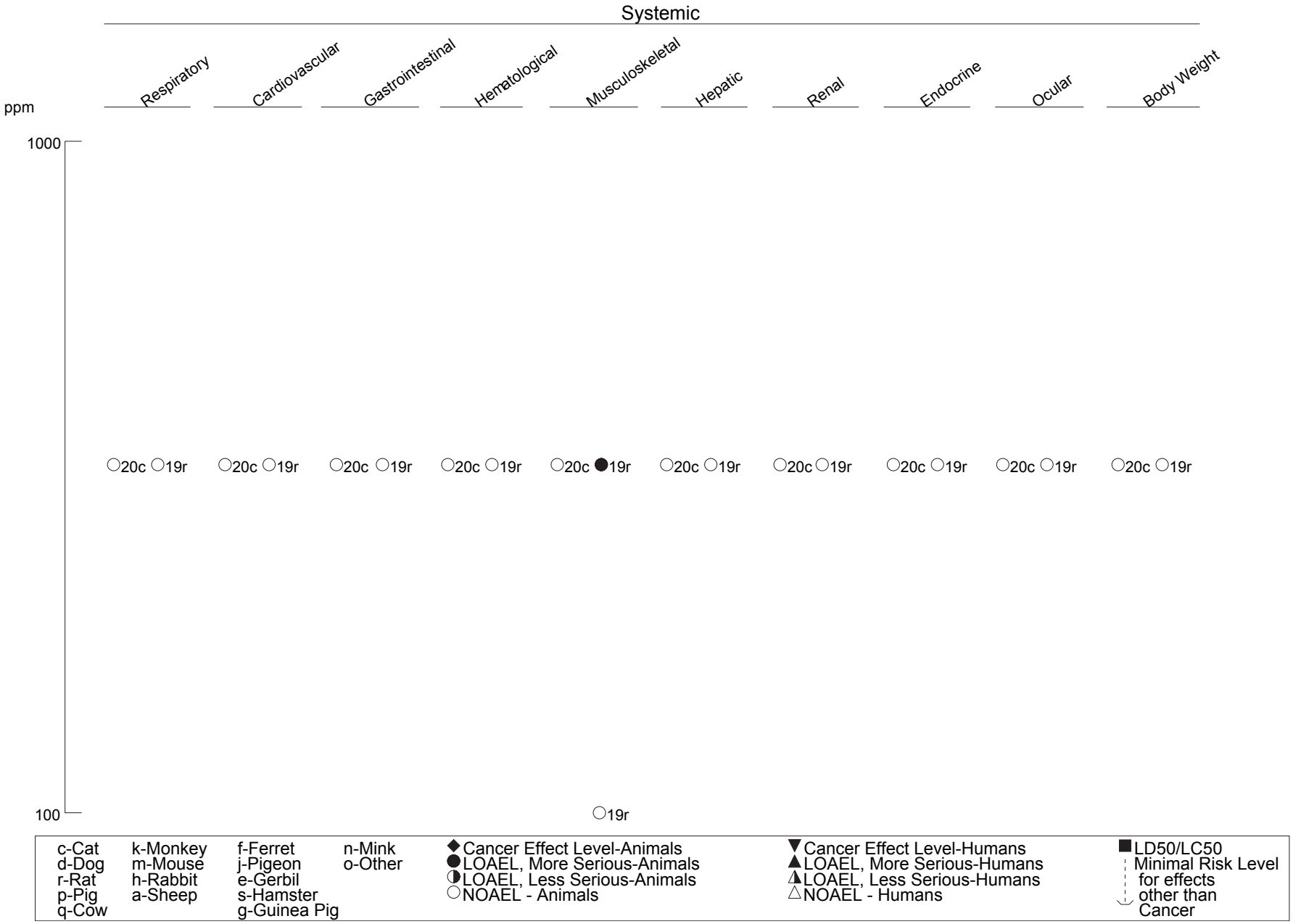
Intermediate (15-364 days)



3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to 2-Hexanone - Inhalation *(Continued)*

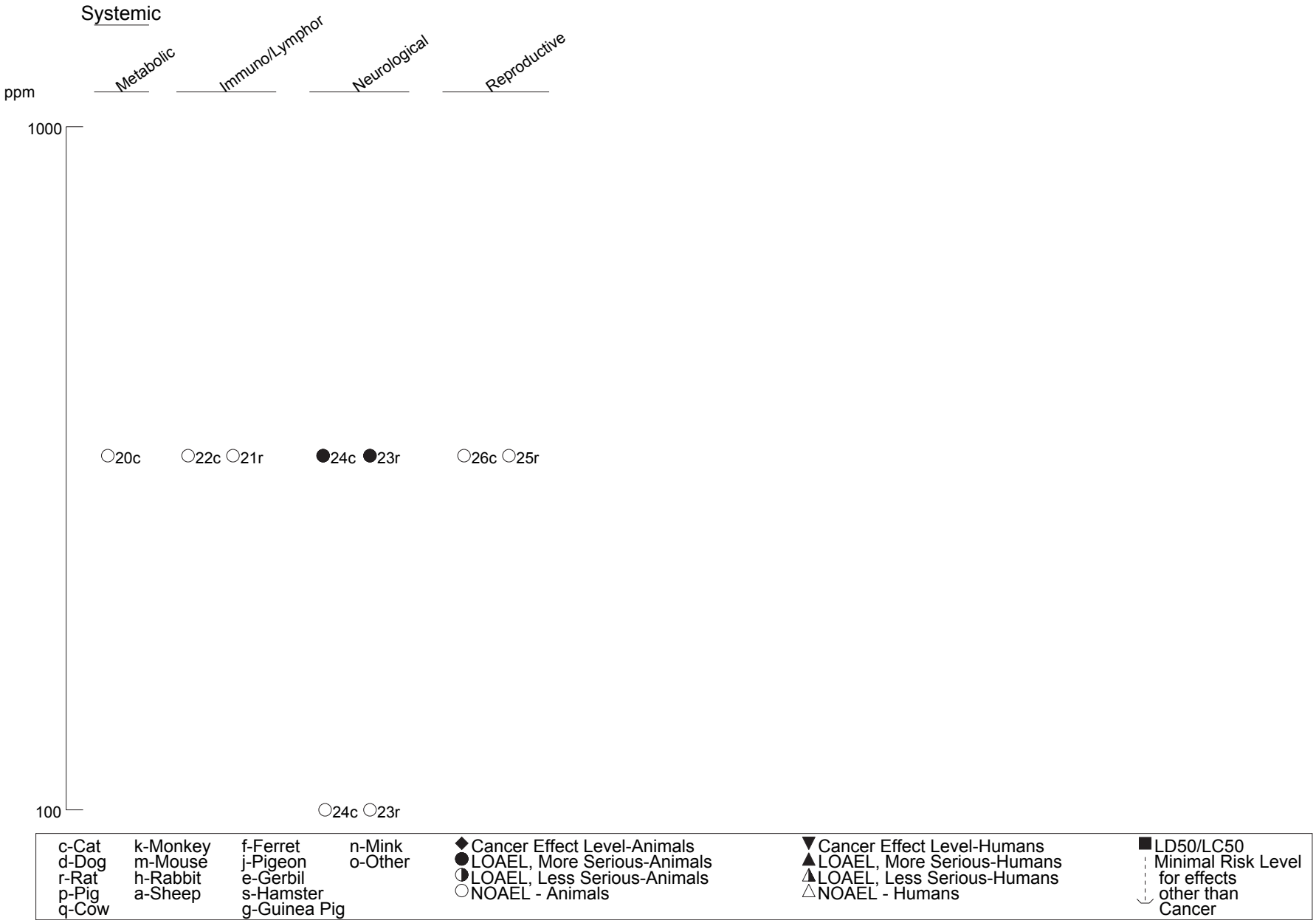
Chronic (≥365 days)



3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to 2-Hexanone - Inhalation *(Continued)*

Chronic (≥365 days)



3.2.1.2 Systemic Effects

The systemic effects observed after inhalation exposure to 2-hexanone are discussed below. The NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, endocrine, dermal, or ocular effects in humans after inhalation exposure to 2-hexanone.

Respiratory Effects. The only relevant information located regarding effects in humans is that from an early study in which men exposed to ≥2,300 ppm 2-hexanone (commercial-grade) vapors for 25–60 seconds considered the contaminated air extremely disagreeable due to a strong odor and irritation of the nasal passages (Schrenk et al. 1936). The same investigators also reported that guinea pigs exposed to 2,300 ppm 2-hexanone showed signs of nose irritation after 1 minute of exposure; no such signs were reported in guinea pigs exposed to 1,000 ppm 2-hexanone.

Limited additional data are available in animals. In intact mice, high concentrations of 2-hexanone showed a mixed pattern of sensory and pulmonary irritation. In cannulated mice, the concentration of 2-hexanone that reduced the respiratory rate by 50% (RD50) during the first 10 minutes of exposure was 6,183 ppm (Hansen and Nielsen 1994). Intermittent whole-body exposure of groups of 18 rats or groups of 4 cats to ≤330 ppm 2-hexanone vapors (purity unknown) 6 hours/day, 5 days/week for 72 weeks or 2 years, respectively, did not induce treatment-related gross or microscopic alterations in the trachea or lungs (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979).

These data show 2-hexanone, at high concentrations in the air, can be a respiratory irritant in humans and in animals. These effects are likely to occur by direct contact of the chemical with mucosal surfaces rather than a systemic mode of action.

Cardiovascular Effects. No significant gross or microscopic alterations were reported in the heart of rats or cats exposed following intermittent whole-body exposure to ≤330 ppm 2-hexanone vapors (purity unknown) for 72 weeks or 2 years, respectively (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979).

Gastrointestinal Effects. Intermittent whole-body exposure of rats or cats to ≤330 ppm 2-hexanone vapors (purity unknown) for 72 weeks or 2 years, respectively, did not induce treatment-related gross or microscopic alterations in the gastrointestinal tract (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979).

Hematological Effects. Limited information is available regarding hematological effects in humans following inhalation exposure to 2-hexanone. In a study of workers exposed to 2-hexanone in a plant producing plastic-coated and color-printed fabrics in Ohio who developed polyneuropathy, hematological tests results were within normal limits, but quantitative data were not shown (Allen et al. 1975).

A significant reduction in total leukocyte counts to about 60% of control values was observed in groups of five rats intermittently exposed to 700 ppm (16 or 20 hours/day for 72 hours/week) (only concentration tested) pure 2-hexanone after 8 weeks of an 11-week study (Katz et al. 1980). Hemoglobin concentration, hematocrit, and differential white cell counts were similar to control values. Although the decrease in total white blood cell counts suggested an effect on bone marrow, the investigators found no microscopic evidence of such damage. Therefore, the clinical significance of their findings is uncertain.

Chronic-duration intermittent whole-body exposure of rats or cats to ≤330 ppm 2-hexanone vapors (purity unknown) did not induce alterations in the bone marrow of the animals (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979); no hematological tests were conducted in these studies that could have helped interpret the findings of the intermediate-duration study of Katz et al. (1980).

The available data are insufficient to assess whether exposure of humans to 2-hexanone represents a risk for hematological effects.

Musculoskeletal Effects. Intermittent whole-body exposure of rats to 330 ppm 2-hexanone vapors (unknown purity) for 72 weeks induced degenerative changes in hindlimb skeletal muscles that resulted in muscle weakness (Krasavage and O'Donoghue 1977). This effect, however, was attributed to damage to the nerves innervating the muscles (see Section 3.2.1.4). No such effect was reported in rats exposed to 100 ppm 2-hexanone. Cats similarly exposed to ≤330 ppm 2-hexanone for 2 years did not develop skeletal muscle alterations (O'Donoghue and Krasavage 1979).

Hepatic Effects. Limited data are available regarding liver effects in humans exposed to 2-hexanone. In the epidemiological study of workers exposed to 2-hexanone of Allen et al. (1975) mentioned above,

clinical tests (liver enzymes, total bilirubin, serum albumin, total protein, serum cholesterol) performed on most workers suspected of a neuropathy were, for the most part, within normal values.

There was no effect on hexobarbital-induced sleep times in rats exposed continuously to 225 ppm 2-hexanone (purity not stated) for 7 days (Couri et al. 1977). Thus, 2-hexanone exposure under these conditions does not seem to affect the hepatic microsomal enzyme activities associated with this response. No histopathological effects were seen in the liver of a group of 40 rats exposed to 50 ppm 2-hexanone (purity not stated) for 6 months (Duckett et al. 1979), or in rats (Krasavage and O'Donoghue 1977) or cats O'Donoghue and Krasavage 1979) exposed chronically to ≤330 ppm 2-hexanone (purity not reported).

The limited data available suggest that the liver is not a primary target for 2-hexanone.

Renal Effects. The only relevant information regarding renal effects in humans is that blood urea nitrogen (BUN) appeared to be low (no quantitative data were provided) in some workers studied by Allen et al. (1975) who had signs of neuropathy. However, the difference between subjects affected with neuropathy and not affected was not significant and there was no correlation between BUN values and severity of the neuropathy.

No histopathological effects were seen in the kidneys of rats exposed to 50 ppm 2-hexanone (purity not stated) for 6 months (Duckett et al. 1979) or in rats (Krasavage and O'Donoghue 1977) or cats O'Donoghue and Krasavage 1979) exposed chronically to ≤330 ppm 2-hexanone (purity not reported).

The limited data available suggest that the kidney is not a primary target for 2-hexanone.

Endocrine Effects. The only relevant information in animals is that no treatment-related histological alterations occurred in the adrenals, thyroid, or parathyroid glands of rats or cats exposed whole-body to ≤330 ppm 2-hexanone vapors (purity not reported) for 72 weeks or 2 years, respectively (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979).

Dermal Effects. No studies were located regarding dermal effects in animals following inhalation exposure to 2-hexanone.

Ocular Effects. An early study by Schrenk et al. (1936) reported that men exposed to ≥2,300 ppm 2-hexanone (commercial-grade) vapors for 25–60 seconds complained of irritation of the eyes (Schrenk et

al. 1936). The investigators also reported that guinea pigs exposed to 2,300 ppm 2-hexanone showed signs of eye irritation after 1 minute of exposure and lacrimation after 10 minutes of exposure; no such signs were reported in guinea pigs exposed to 1,000 ppm 2-hexanone. These effects in humans and guinea pigs are probably due to direct contact of 2-hexanone vapors with the eye surface rather than via a systemic mode of action.

A long-term exposure study reported that no treatment-related ocular effects were reported in rats or cats exposed whole-body to ≤330 ppm 2-hexanone vapors (purity not reported) (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979).

Body Weight Effects. A 1973 outbreak of distal polyneuropathy involving 86 of 1,157 employees was reported in a plant that had been using 2-hexanone for about 10 months in the production of plastic-coated and color-printed fabrics (Allen et al. 1975; Billmaier et al. 1974) (neurological effects associated with this exposure are discussed in Section 3.2.1.4). Clinical evaluations indicated that of 10 workers whose body weight was recorded, weight loss ranging from 3 to 60 pounds was observed in the eight workers found to have moderate to severe neurological impairment (Allen et al. 1975). Of the milder cases, no significant weight change could be correlated with the presence of the disorder. Atmospheric sampling conducted after this incident indicated that 2-hexanone levels averaged 9.2 ppm in front of the printing machines and 36 ppm behind the machines. After the use of 2-hexanone was discontinued, weight gain was uniformly noted in those who had lost weight. It is not clear whether the affected individuals had decreased appetites and/or food consumption levels in conjunction with their weight loss.

Intermediate-duration studies have reported decreases in body weight in animals exposed to 2-hexanone. A NOAEL of 100 ppm was reported in rats in two studies (Egan et al. 1980; Johnson et al. 1977). In the former study, which tested pure 2-hexanone in rats exposed for 22 hours/day, 7 days/week, for 6 months, 100 ppm was the only concentration tested, whereas Johnson et al. (1977), who tested a commercial-grade 2-hexanone of unknown purity in rats exposed for 6 hours/day, 5 days/week for 15 weeks, reported a LOAEL of 1,000 ppm in rats. These rats displayed progressive weight loss, which became statistically significant at 20 weeks. The NOAEL was 100 ppm. In another intermediate-duration study in rats, exposure for 16 or 20 hours/day for 72 hours/week to 700 ppm (only level tested) pure 2-hexanone induced a marked reduction in weight gain within 3 days of exposure (Katz et al. 1980). Johnson et al. (1977) also tested monkeys and reported that exposure to 1,000 ppm 2-hexanone induced a progressive nonsignificant loss of body weight beginning 4 months after exposure started; 100 ppm did not induce significant effects.

In a developmental study, weight gain decrements of 10 and 14% relative to controls were reported in groups of 25 pregnant rats exposed to 1,000 or 2,000 ppm 2-hexanone, respectively, 6 hours/day during 21 days of gestation (Peters et al. 1981). No body weight effects were seen in dams exposed to 500 ppm. However, no statistical analysis was performed on these results. Rats in the 2,000 ppm exposure group were observed to eat less than controls, but no quantitative data were presented.

Exposure of rats and cats to ≤330 ppm 2-hexanone (purity unknown) for 72 weeks or 2 years, respectively, did not result in significant alterations in body weight (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979).

In the absence of any information regarding food consumption, the toxicological significance of most of the data summarized above is unknown.

Metabolic Effects. Levels of serum glucose, inorganic phosphorus, and calcium were within normal limits in workers exposed to 2-hexanone in a plant producing plastic-coated and color-printed fabrics in Ohio who developed polyneuropathy (Allen et al. 1975). No further information was located.

The only relevant information available in animals is that cats had normal serum levels of calcium, sodium, potassium, and chloride 140 days after intermittent whole-body exposure to ≤330 ppm 2-hexanone (purity unknown) vapors (O'Donoghue and Krasavage 1979).

These limited data are insufficient to draw any conclusions regarding exposure to 2-hexanone and metabolic effects.

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after inhalation exposure to 2-hexanone.

The only relevant information in animals is that intermittent whole-body exposure of rats or cats to ≤330 ppm 2-hexanone vapors (unknown purity) for 72 weeks or 2 years, respectively, did not induce gross or microscopic alterations in the spleen, thymus, or lymph nodes (Krasavage and O'Donoghue

1977; O'Donoghue and Krasavage 1979). No tests of immunocompetence were conducted in these studies.

The available studies do not provide sufficient information to assess possible adverse immunological effects due to exposure to 2-hexanone.

The 330 ppm exposure levels are listed as NOAELs for lymphoreticular effects in rats and cats in Table 3-1 and are plotted in Figure 3-1.

3.2.1.4 Neurological Effects

In humans, the most important effect associated with inhalation exposure to 2-hexanone is neurological dysfunction, most commonly observed as peripheral neuropathy. Reported effects in human studies include a peripheral neuropathy characterized by axon and myelin disruption and axonal swellings involving motor and sensory nerves and resulting in alterations in nerve conduction velocity, ataxia, sensory deficits, and skeletal muscle weakness accompanied by electromyographic abnormalities. Widespread attention was brought to this phenomenon after a 1973 outbreak of distal neuropathy in an Ohio fabric finishing plant that had introduced the use of 2-hexanone into its processing operations approximately 10 months before the first cases of neuropathy were reported. The time worked in the print department by persons with peripheral neuropathy ranged from 5 weeks to 27 years. The screening of 1,157 employees resulted in the detection of 86 verified cases of neuropathy (Allen et al. 1975; Billmaier et al. 1974). Eleven of these cases were moderate to severe with both motor and sensory involvement; 38 were mild with sensory signs prevailing; and 37 were considered minimal, without clinical manifestations but with characteristic electrodiagnostic abnormalities. General characteristics of the neuropathy included muscle weakness, sensory loss (inability to discriminate pain, touch, temperature, or vibration) in the hands and feet, and diminution or loss of reflexes. Electromyographic testing generally indicated that nerve conduction velocities were slower, especially in the ulnar, peroneal, tibial, and sural nerves, and the distal latencies (times to response) were prolonged in parallel to the reduction of the nerve conduction velocity. Other abnormalities included waves and fibrillations, especially in the more severe cases, and a decrease in the number and an increase in the size of motor unit potentials. No histological evidence of nerve damage was obtained in any of these patients. Atmospheric sampling conducted after this incident indicated that 2-hexanone levels in the processing plant averaged 9.2 ppm in front of the printing machines, 36 ppm behind them, and 6.1 ppm in the wind-up area. The operators spent 60–80% of their time in front of the printing machines (mean 9.2 ppm). After the use of 2-hexanone was

discontinued, marked improvement was seen in the affected employees during the next few months, including all of the moderate-to-severe cases and most of the mild and minimal cases. It should be noted that significant exposure to MEK also occurred. While MEK does not induce neuropathy by itself, it has been shown to potentiate the effects induced by 2-hexanone (Saida et al. 1976). Also worth mentioning is that dermal and oral exposure was likely to have occurred due to practices such as eating in/on work areas or washing the hands in solvent.

Mallov (1976) reported three cases of severe peripheral neuropathy among 26 spray painters at one work site. In two cases, exposure to 2-hexanone was the most likely cause of the condition; in the third case, exposure to 2-hexanone was the probable cause. Davenport et al. (1976) also reported a case of peripheral neuropathy in a subject exposed to 2-hexanone at work; in this case, there was also exposure to other compounds, including MiBK.

Numerous studies have been conducted in hens/chickens as this species has proved to be a good, sensitive model for 2-hexanone-induced neuropathy. However, while studies of hens/chickens are useful for hazard identification, they are not useful for risk assessment. Because their digestive and respiratory systems are different from mammals, it is not known whether the dose-response in this species is applicable to humans.

In all animal species studied, including monkeys, cats, rats, and chickens, the clinical observations generally indicated a progression from weakness and ataxia to complete paralysis of the limbs. These clinical observations were accompanied or preceded by morphological changes in the peripheral nerves, including an increase in the number of neurofilaments in the nerve fibers, axonal swelling, and inpouchings and thinning of the myelin sheath. Studies in animals also show involvement of the central nervous system. Studies that have examined the metabolic disposition of 2-hexanone have shown that the chemical entity responsible for the neurotoxic effects of 2-hexanone is 2,5-hexanedione, a metabolite of 2-hexanone in rats, guinea pigs, and humans (Abdel-Rahman et al. 1978; DiVincenzo et al. 1976, 1978; Eben et al. 1979). Comparative studies of the relative neurotoxicities of 2-hexanone, 2,5-hexanedione, and other compounds have concluded that 2,5-hexanedione is a more potent neurotoxicant than 2-hexanone (Abou-Donia et al. 1982; Krasavage et al. 1980). Comparative studies also have shown the relative species sensitivity to 2-hexanone as chicken > cat > dog > primate > rat (Abdo et al. 1982; Mendell et al. 1974b).

Limited data regarding acute exposure were located. Schrenk et al. (1936) reported that exposure of guinea pigs to 2,300 ppm commercial-grade 2-hexanone for 90 minutes produced incoordination; no adverse clinical signs were seen in guinea pigs exposed to 1,000 ppm 2-hexanone for up to 810 minutes. In another study, severe neurotoxicity was reported in rats as a result of 7 days of continuous inhalation exposure to 225 ppm (only concentration tested) 2-hexanone of unknown purity (Couri et al. 1977). No further details were provided in this study.

Intermediate-duration inhalation studies provide data on neurotoxicity of 2-hexanone in rats, cats, and monkeys. Evaluation of the data, however, is complicated because several studies tested only one exposure level, which caused neurotoxicity, so NOAELs were not defined. In addition, the true LOAEL was probably lower than the exposure level tested. Furthermore, in most studies, the purity of the compound tested was not stated and it could have varied between 70 and 98% 2-hexanone.

Intermediate-duration studies in rats reported neuropathies that affected axons and the myelin sheath; axonal swelling was commonly seen (Duckett et al. 1979; Egan et al. 1980; Mendell et al. 1974b; Saida et al. 1976; Spencer et al. 1975). These effects can lead to nerve degeneration. The lowest LOAEL was histopathological effects in rats was 50 ppm 2-hexanone (unknown purity), the only exposure level tested (Duckett et al. 1979). Histopathological changes were usually accompanied by signs such as weakened hindlimbs (Katz et al. 1980) and forelimbs (Spencer et al. 1975), hindlimb dragging (Mendell et al. 1974b), and even paralysis (Saida et al. 1976). In general, the higher the exposure concentration, the earlier the effects appeared. Electrophysiological tests conducted in one study showed significantly decreased motor nerve conduction velocity in the sciatic-tibial nerve after intermittent exposure to ≥100 ppm commercial-grade (unknown purity) 2-hexanone for 29 weeks (Johnson et al. 1977). The latter study also reported impaired operant behavioral performance in rats exposed to 1,000 ppm 2-hexanone (highest concentration tested). Alterations in the central nervous system were also reported in rats after 4 months of exposure to 100 ppm (only concentration tested) pure 2-hexanone 22 hours/day (Egan et al. 1980); lesions included giant axonal swellings in the medulla oblongata and cerebellum. Similar findings were reported in cats and monkeys exposed repeatedly to 2-hexanone for intermediate durations. In monkeys, 100 ppm (lowest concentration tested) commercial-grade 2-hexanone (unknown purity) was a LOAEL for reduced conduction velocity in the sciatic-tibial nerve (Johnson et al. 1977). In cats, continuous exposure to 400–600 ppm 2-hexanone (unknown purity) induced hind limb dragging followed by forelimb weakness and eventual paralysis (Mendell et al. 1974b). Morphological evaluations showed axonal swelling and demyelination of nerve fibers. In both cats and monkeys, recovery occurred months after exposure to 2-hexanone ceased.

Chronic-duration studies in rats and cats showed equivocal clinical and morphological signs of neuropathy in rats exposed intermittently (6 hours/day, 5 days/week) to 330 ppm 2-hexanone vapors for 72 weeks (Krasavage and O'Donoghue 1977) and clear morphological signs of neuropathy in cats similarly exposed to 330 ppm 2-hexanone for 2 years (O'Donoghue and Krasavage 1979). No signs of neuropathy were reported in rats or cats exposed to 100 ppm 2-hexanone. In neither study was the purity of 2-hexanone stated. Poor reporting of the results made it difficult to establish a NOAEL and LOAEL in the rat study; however, rats exposed to 330 ppm showed degenerative changes in skeletal muscle that were most likely due to neuropathy in the innervating nerve fibers. No clinical neurological signs were reported in the cats, but all cats in the 330 ppm exposure group showed lesions in the peripheral and central nervous system at and below the levels of the cerebellum and pons. In the periphery, sciatic nerve axons showed organelle accumulations with rare focal discrete "giant" axonal swelling that also involved the myelin. The sensory portion of the peripheral nervous system was least affected. Neuropathological effects in the central nervous system were generally minor; swollen terminals were found in the posterior cerebellar peduncles, folial white matter, nucleus gracilis, fasciculus gracilis, spino-cerebellar tracts, medullary reticular formation, and all levels of the spinal cord. Detailed examination of tibial nerve fibers showed a higher percentage of demyelinated, re-myelinated, swollen, and degenerative fibers in the high-exposure group than in controls and low-exposure groups.

The data available suggest that exposure to 2-hexanone was probably the cause of adverse neurological effects in the occupational studies mentioned above. Studies in animals indicate that the nervous system is a primary target for 2-hexanone and effects in animals are consistent with those reported in subjects occupationally exposed to 2-hexanone.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species in the intermediate-duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

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

Limited data exist in animals. Marked and significant reductions in absolute and relative testes weight and atrophy of testicular germinal epithelium were observed in male rats exposed to 700 ppm 2-hexanone (96.1% pure) for 11 weeks (Katz et al. 1980); no other exposure level was tested in this study.

Chronic-duration exposure of male rats or female cats to ≤330 ppm 2-hexanone (unknown purity) did not induce compound-related gross or microscopic alterations in the reproductive organs of either species (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979).

The data available are insufficient to determine whether exposure to 2-hexanone could adversely affect reproduction in humans.

The LOAEL value from the intermediate-duration study and the NOAELs from the chronic-duration studies are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

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

Intermittent exposure of groups of 25 pregnant rats to 2,000 ppm 2-hexanone (unknown purity) 6 hours/day during the entire gestation period resulted in a significant reduction in the number of pups per litter and in neonatal weight (40%); no such effects were reported in rats exposed to 1,000 ppm (Peters et al. 1981). In this study, behavioral alterations consisting of reduced activity in the open field, increased activity in the running wheel, and deficits in avoidance conditioning were reported in the offspring of exposed dams at all ages (newborn, weanling, puberty, and adult) except geriatric in which results were similar to those of controls. Behavioral tests in most cases indicated that maternal exposure to 2-hexanone was associated with hyperactivity in the young and decreased activity in the geriatric stage, which the authors speculated to be due to premature aging resulting from the earlier hyperactivity. It is not clear whether these effects are the result of transplacental exposure to 2-hexanone or of postnatal exposure to 2-hexanone and/or its metabolites via the milk of the exposed dams.

No firm conclusions can be made regarding developmental effects of 2-hexanone based on a single animal study; further information would be necessary.

The LOAEL values for developmental effects in rats in the intermediate duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.7 Cancer

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

3.2.2 Oral Exposure

3.2.2.1 Death

An LD_{50} of 2,590 mg/kg was calculated for a gavage administration of 2-hexanone (purity not stated) to Wistar rats, sex was not specified (Smyth et al. 1954).

The LD_{50} value from Smyth et al. (1954) is recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The systemic effects observed after oral exposure to 2-hexanone are discussed below. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

No studies were located regarding systemic effects in humans after oral exposure to 2-hexanone. The results from studies in animals suggest that the systemic end points mentioned below are not primary targets for 2-hexanone except for skeletal muscle, which can develop alterations of neurogenic origin.

Respiratory Effects. Exposure of groups of 5 female rats to ≤1,010 mg 2-hexanone kg/day (assumed to be pure) for 120 days (Union Carbide 1977) or of groups of 10 rats (sex not specified) to ≤560 mg pure 2-hexanone/kg/day for 13 months via the drinking water did not induce gross or microscopic lesions in the lungs or trachea (O'Donoghue et al. 1978).

Cardiovascular Effects. Treatment of rats with ≤1,010 mg 2-hexanone/kg/day for 120 days (Union Carbide 1977) or to ≤560 mg pure 2-hexanone/kg/day for 13 months via the drinking water did not induce gross or microscopic lesions in the heart (O'Donoghue et al. 1978).

Table 3-2 Levels of Significant Exposure to 2-Hexanone - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Wistar)	once (G)				2590 (LD50)	Smyth et al. 1954 UNKNOWN	
Systemic								
2	Rat (Fischer- 344)	once (GO)	Hepatic	1500 M			Brown and Hewitt 1984 PURE	Liver NOAEL is for liver histology.
			Renal		1500 M (tubular degeneration in some rats)			
INTERMEDIATE EXPOSURE								
Systemic								
3	Rat (Wistar)	40 wk 1x/d (GW)	Hepatic	400 M			Eben et al. 1979 PURE	NOAELs are for liver and kidney function.
			Renal	400 M				
4	Rat	90 d 5 d/wk 1 x/d (G)	Bd Wt			660 M (39% reduced body weight)	Krasavage et al. 1980 PURE	

Table 3-2 Levels of Significant Exposure to 2-Hexanone - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
5	Rat (Wistar)	120 d ad lib (W)	Resp	1010 F			Union Carbide 1977 UNKNOWN	NOAELs are for tissue or organ histopathology.
			Cardio	1010 F				
			Gastro	1010 F				
			Musc/skel			480 F (skeletal muscle atrophy)		
			Hepatic	1010 F				
			Renal	1010 F				
			Endocr	1010 F				
			Ocular	1010 F				
			Bd Wt			480 F (46% reduction in body weight gain)		
Immuno/ Lymphoret								
6	Rat (Wistar)	120 d ad lib (W)		1010 F			Union Carbide 1977 UNKNOWN	NOAEL is for histopathology of lymphoreticular tissues.
Neurological								
7	Rat (Wistar)	40 wk 1x/d (GW)			400 M (hindlimb weakness)		Eben et al. 1979 PURE	No histological examinations were conducted.
8	Rat	90 d 5 d/wk 1 x/d (G)				660 M (paralysis, histopathology)	Krasavage et al. 1980 PURE	

Table 3-2 Levels of Significant Exposure to 2-Hexanone - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
9	Rat (Wistar)	120 d ad lib (W)				480 F (peripheral neuropathy)	Union Carbide 1977 UNKNOWN	
10	Gn Pig (English short hair)	24 wk (W)				310 (40% reduction in locomotor activity)	Abdel-Rahman et al. 1978 UNKNOWN	Exposure to 2-hexanone also reduced pupillary responses to light stimuli.
Reproductive								
11	Rat (Wistar)	120 d ad lib (W)		1010 F			Union Carbide 1977 UNKNOWN	NOAEL is for histopathology of the uterus and ovaries.

Table 3-2 Levels of Significant Exposure to 2-Hexanone - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
12	Rat (Sprague-Dawley)	13 mo ad lib (W)	Resp	560 M			O'Donoghue et al. 1978 PURE	NOAELs are for organ histopathology.
			Cardio	560 M				
			Gastro	560 M				
			Musc/skel	143 M	266 M (skeletal muscle myofiber atrophy)			
			Hepatic	560 M				
			Renal	560 M				
			Endocr	560 M				
			Ocular	560 M				
			Bd Wt	143 M	266 M (14% reduced final weight)	560 M (36% reduced final weight)		
Immuno/ Lymphoret								
13	Rat (Sprague-Dawley)	13 mo ad lib (W)		560 M			O'Donoghue et al. 1978 PURE	NOAEL is for spleen and thymus histopathology.
Neurological								
14	Rat (Sprague-Dawley)	13 mo ad lib (W)			143[b] M (peripheral nerve axonal swelling)	266 M (axonal and myelin degeneration)	O'Donoghue et al. 1978 PURE	

Table 3-2 Levels of Significant Exposure to 2-Hexanone - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
15	Rat (Sprague-Dawley)	13 mo ad lib (W)		560 M			O'Donoghue et al. 1978 PURE	NOAEL is for testes and epididymis histopathology.

a The number corresponds to entries in Figure 3-2.

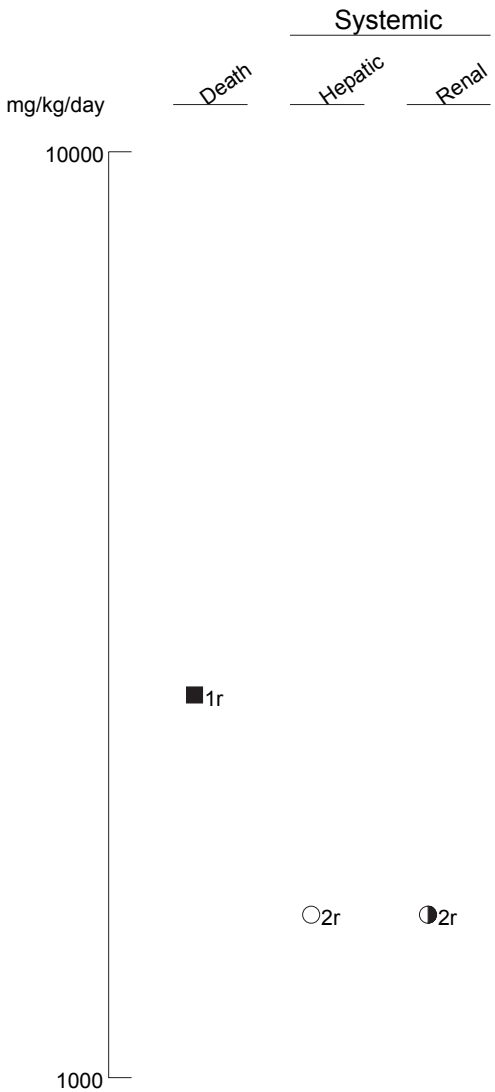
b Used to derive a chronic-duration oral (MRL) of 0.05 mg/kg/day for 2-hexanone. The MRL was calculated by dividing the LAOEL of 143 mg/kg/day for axonal swelling in peripheral nerve of male rats by a combined uncertainty factor of 3,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, 10 for human variability, and 3 to account for a response rate of 80% at the lowest dose).

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; (G) = gavage; Gastro = gastrointestinal; (GO) = gavage in oil; Gn pig = guinea pig; (GW) = gavage in water; Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; x = time(s); (W) = drinking water; wk = week(s)

3. HEALTH EFFECTS

Figure 3-2 Levels of Significant Exposure to 2-Hexanone - Oral

Acute (≤14 days)



c-Cat, d-Dog, r-Rat, p-Pig, q-Cow; k-Monkey, m-Mouse, h-Rabbit, a-Sheep; f-Ferret, j-Pigeon, e-Gerbil, s-Hamster, g-Guinea Pig; n-Mink, o-Other

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

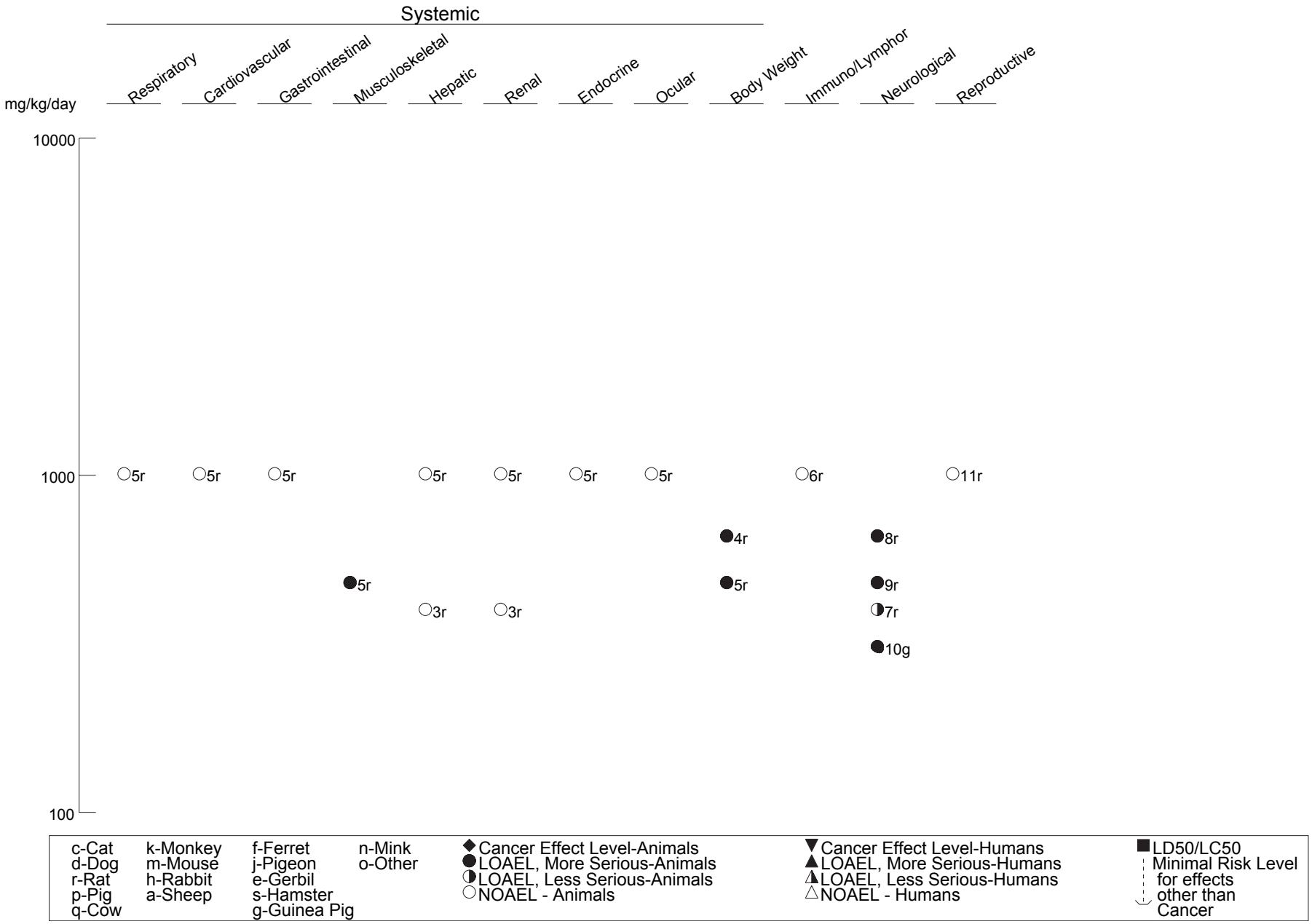
▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

3. HEALTH EFFECTS

Figure 3-2 Levels of Significant Exposure to 2-Hexanone - Oral *(Continued)*

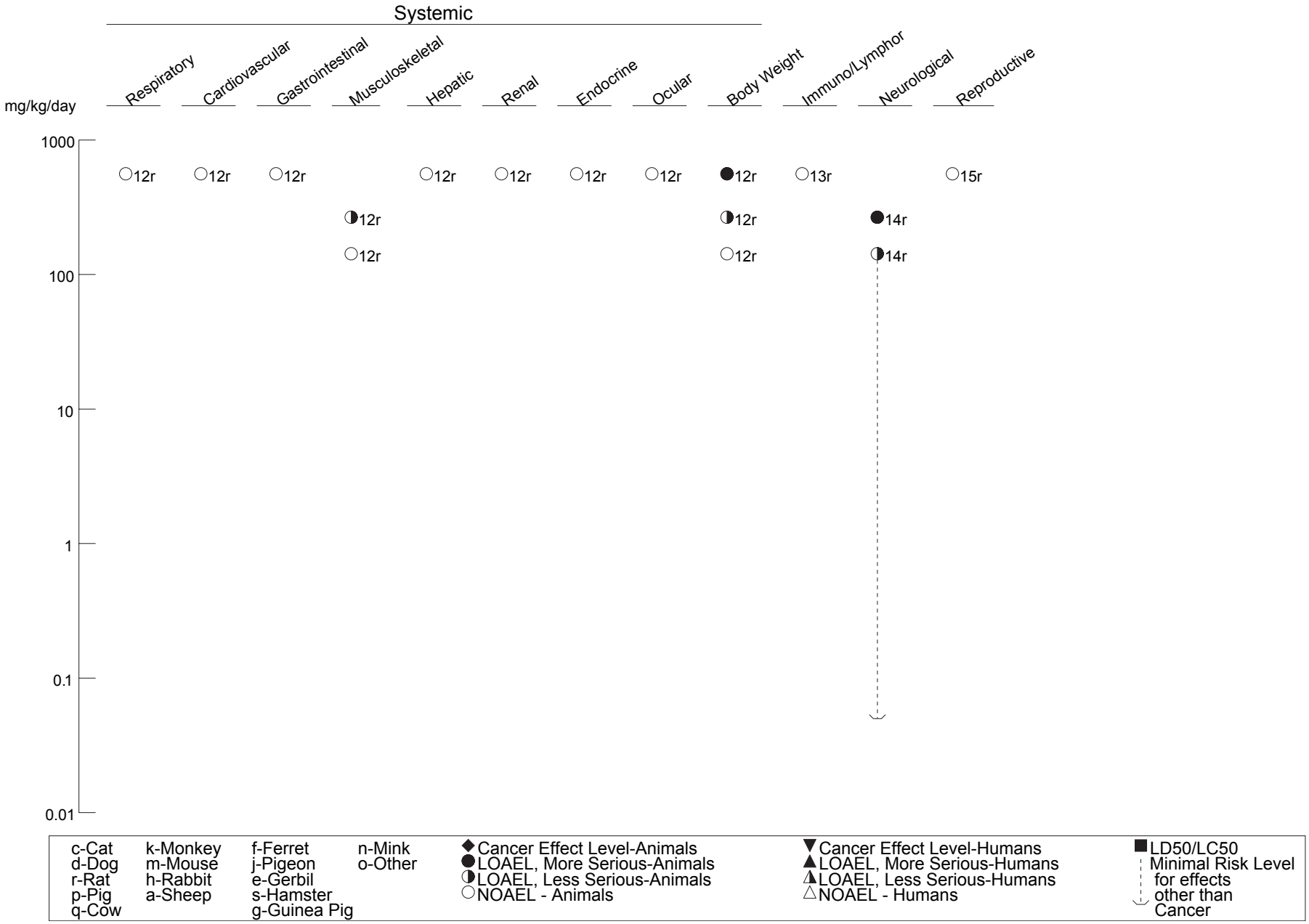
Intermediate (15-364 days)



3. HEALTH EFFECTS

Figure 3-2 Levels of Significant Exposure to 2-Hexanone - Oral *(Continued)*

Chronic (≥365 days)



Gastrointestinal Effects. Examination of the gastrointestinal tract of rats exposed to ≤1,010 mg 2-hexanone/kg/day for 120 days or to ≤560 pure 2-hexanone/kg/day for 13 months through the drinking water did not reveal treatment-related gross or microscopic lesions (O'Donoghue et al. 1978; Union Carbide 1977).

Hematological Effects. No information was located regarding hematological effects in animals following oral exposure to 2-hexanone.

Musculoskeletal Effects. Skeletal muscle pathology of neurogenic origin was reported in rats following exposure to ≥480 mg 2-hexanone/kg/day for 120 days (Union Carbide 1977). Similar findings were reported in rats dosed with ≥266 mg pure 2-hexanone/kg/day for 13 months via the drinking water (O'Donoghue et al. 1978). Gross pathology was limited to atrophy of skeletal muscles of the hind limbs and lumbar muscles. Light microscopy showed significant treatment-related alterations of neurogenic skeletal muscle atrophy in proximal and distal hind limb musculature of high-dose rats. Alterations in rats treated with 266 mg 2-hexanone/kg/day were similar but less severe; no significant alterations were reported at 143 mg 2-hexanone/kg/day.

Hepatic Effects. Limited data are available regarding hepatic effects of 2-hexanone in animals. These studies suggest that the liver is not a primary target for 2-hexanone. A single gavage dose of 1,500 mg pure 2-hexanone/kg (only dose tested) did not produce histological changes in livers from rats (Brown and Hewitt 1984). In a 40-week study in a group of 60 rats administered daily gavage doses of 400 mg pure 2-hexanone/kg/day (only dose level tested), periodic assessments of serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) showed values within normal limits (Eben et al. 1979). 2-Hexanone (purity unknown) did not affect liver morphology in rats administered doses of ≤1,010 mg/kg/day for 120 days (Union Carbide 1977). The lack of histopathology was also confirmed in a 13-month drinking water study in rats that received doses of ≤560 mg pure 2-hexanone/kg/day (O'Donoghue et al. 1978).

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

Limited data in animals suggest that the kidney is not a primary target for 2-hexanone. A single gavage dose of 1,500 mg 2-hexanone/kg (only dose tested) produced tubular degeneration in rats (Brown and

Hewitt 1984), but no quantitative data were provided. 2-Hexanone (unknown purity) did not induce gross or microscopic changes in the kidneys of rats when given doses of ≤1,010 mg/kg/day for 120 days (Union Carbide 1977). In another intermediate-duration study, periodic assessments of plasma urea and creatinine, as indices of kidney function, in rats administered 400 mg pure 2-hexanone/kg/day (only dose level tested) by gavage for 40 weeks revealed values within normal limits (Eben et al. 1979). Exposure of rats for 13 months to ≤560 mg pure 2-hexanone/kg/day in the drinking water did not induce gross or microscopic alterations in the kidneys (O'Donoghue et al. 1978).

Endocrine Effects. No studies were located regarding endocrine effects in humans following oral exposure to 2-hexanone.

The only information regarding effects in animals is that exposure of rats to ≤1,010 mg 2-hexanone/kg/day for 120 days (Union Carbide 1977) or to ≤560 mg pure 2-hexanone/kg/day for 13 months did not induce gross or microscopic alterations in adrenals, thyroid, or parathyroid glands, or the pancreas (O'Donoghue et al. 1978). In both studies, 2-hexanone was administered in the drinking water.

Dermal Effects. No studies were located regarding dermal effects in humans or animals following oral exposure to 2-hexanone.

Ocular Effects. The only relevant information available is that administration of ≤1,010 mg 2-hexanone/kg/day to female rats via the drinking water for 120 days (Union Carbide 1977) or ≤560 mg pure 2-hexanone/kg/day in the drinking water for 13 months did not induce treatment-related alterations in the eyes (O'Donoghue et al. 1978). No additional information was located.

Body Weight Effects. Reductions in weight gain were reported in rats in intermediate- and chronic-duration studies. In the former, a group of 5 rats given doses of 660 mg pure 2-hexanone/kg/day (only dose tested) by gavage 5 days/week over 90 days weighed about 61% of control rats by 10 weeks of exposure (Krasavage et al. 1980). Treated rats consumed approximately 18% less food (g/rat/day) than control rats, which would suggest that factors other than the reduced food consumption played a role in the reduced weight gain. Similar results were reported in a 120-day drinking water study in rats (Union Carbide 1977). In the chronic study, rats dosed with 266 or 560 mg pure 2-hexanone/kg/day weighed 14% and 36% less than control rats, respectively, after 13 months of treatment (O'Donoghue et al. 1978),

and doses of 143 mg/kg/day did not significantly affect weight gain; no data on food consumption were provided in this study.

Metabolic Effects. No studies were located regarding metabolic effects in animals following oral exposure to 2-hexanone.

3.2.2.3 Immunological and Lymphoreticular Effects

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

The only information regarding effects in animals is that exposure of rats to ≤1,010 mg 2-hexanone/kg/day for 120 days (Union Carbide 1977) or to ≤560 mg pure 2-hexanone/kg/day in the drinking water for 13 months did not induce gross or microscopic alterations in the spleen or thymus (O'Donoghue et al. 1978). This information is insufficient to draw any conclusions regarding possible immunological effects in humans following oral exposure to 2-hexanone.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to 2-hexanone, but based on results from oral studies in animals and on what is known regarding the toxicokinetics of 2-hexanone in humans and in animals, adverse neurological effects will likely occur in humans following high oral exposure to this chemical.

As mentioned earlier, numerous studies have been conducted in hens/chickens as this species has proved to be a good sensitive model for 2-hexanone-induced neuropathy. However, while studies of hens/chickens are useful for hazard identification, they are not useful for risk assessment because it is not known whether the dose-response in this species is applicable to humans.

Repeated oral exposure of animals to 2-hexanone causes the same type of neurological effects observed after inhalation exposure, which is not unexpected since both routes of exposure give rise to the toxic entity, 2,5-hexanedione. Information is available from intermediate- and chronic-duration studies.

Intermediate-duration studies provided LOAELs for clinical signs and morphological alterations in the peripheral nervous system but NOAELs were not identified. In rats, doses of 400 mg 2-hexanone/kg/day (only dose tested) induced transient weakness of the hindlimbs on weeks 17 to 28 of a 40-weeks study

(Eben et al. 1979), and doses of ≥480 mg 2-hexanone/kg/day induced clinical signs such as muscle weakness and hindlimb dragging (Krasavage et al. 1980; Union Carbide 1977). In these two studies (Krasavage et al. 1980; Union Carbide 1977), microscopic examination of peripheral nerves showed evidence of neuropathy involving both axons and the myelin sheath. No histological examinations were conducted by Eben et al. (1979). Both Eben et al. (1979) and Krasavage et al. (1980) used high purity 2-hexanone. A 40% decrease in locomotor activity was reported in groups of five guinea pigs given 2-hexanone of unknown purity in drinking water at dosage levels of approximately 310 mg 2-hexanone/kg/day during a 24-week study (Abdel-Rahman et al. 1978). Reduced pupillary responses to light (measured by changes in pupillary diameter) were also reported in this study. However, no information was provided regarding effects that may have occurred at a lower exposure level of approximately 124 mg 2-hexanone/kg/day.

In the single chronic-duration (13-month) study available for review, the lowest dose of 2-hexanone (high purity) tested, 143 mg/kg/day, caused axonal swellings in peripheral nerves of rats (O'Donoghue et al. 1978). Clinical neurological signs were seen in rats dosed with ≥266 mg 2-hexanone/kg/day and first appeared on day 42 in the rats dosed with 560 mg/kg/day and on day 77 in rats dosed with 266 mg/kg/day. Signs included decreased extension of hindlimbs, hindlimb weakness, waddling gait, dragging of hind paws, and loss of tone in hindlimb musculature with grossly observable atrophy of hindlimb musculature and axial muscles of the lumbar area. Histological examinations showed that rats from all treated groups had "giant' axonal neuropathy. Axonal swelling and giant axonopathy were common in peripheral nerves and spinal cord, less common in dorsal root ganglia, and rare in the brain. Myelin alterations were also seen in peripheral nerves. Neurogenic skeletal muscle atrophy occurred in proximal and distal hindlimb musculature. Alterations in the mid-dose group were similar but less severe. Less severe changes were seen in peripheral nerves from low-dose rats; fewer giant axons were evident, but myelin changes were more common. Spinal lesions and neurogenic muscle atrophy were minimal. Results from this study were used to derive a chronic-duration oral provisional MRL for 2-hexanone.

LOAEL values from the studies summarized above are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to 2-hexanone.

Male rats that were given 2-hexanone (96.1% pure) at 660 mg/kg/day (only dose tested) by gavage in a 90-day study were reported to develop atrophy of the germinal epithelium of the testes (Krasavage et al. 1980). However, no quantitative data were presented, so this effect is not listed in Table 3-2. The only additional relevant information regarding reproductive effects of 2-hexanone in animals is that treatment of female rats with ≤1,040 mg 2-hexanone/kg/day for 120 days (Union Carbide 1977) or male rats with ≤560 mg 2-hexanone/kg/day (96.1% pure) via drinking water for 13 months did not induce gross or microscopic alterations in the reproductive organs (O'Donoghue et al. 1978). The dose levels of 560 and 1,010 mg 2-hexanone/kg/day are listed as NOAELs for reproductive effects in Table 3-2 and are plotted in Figure 3-2.

The available data suggest that environmental levels of 2-hexanone (mostly water levels reported in the past, ppb range) do not represent a reproductive risk for humans.

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

3.2.2.6 Developmental Effects
3.2.2.7 Cancer

3.2.3 Dermal Exposure

Very little information is available regarding dermal effects of 2-hexanone in humans. Schrenk et al. (1936) reported that men exposed to ≥2,300 ppm of a commercial-grade of 2-hexanone for 25–60 seconds considered the contaminated air extremely disagreeable due to a strong odor and irritation of the eyes and nasal passages.

The same investigators also reported that guinea pigs exposed to 2,300 ppm 2-hexanone showed signs of eye and nose irritation after 1 minute of exposure and lacrimation after 10 minutes of exposure; no such signs were reported in guinea pigs exposed to 1,000 ppm 2-hexanone (Schrenk et al. 1936). It should be noted that these effects in humans and in guinea pigs are assumed to have been due to direct contact of the vapors with the tissues rather than through a systemic mode of action. In another study, application of undiluted 2-hexanone to the skin of rabbits for 24 hours resulted in Grade 1 (least severe) irritation and that ocular instillation resulted in Grade 3 (moderate) corneal necrosis (Smyth et al. 1954).

3.3 GENOTOXICITY

No studies were located regarding the potential genotoxic effects in humans or animals following any route of exposure to 2-hexanone. One study was located that provided data on genotoxicity of 2-hexanone in an *in vitro* system. The study reported that 2-hexanone was mutagenic in *Salmonella typhimurium* 1535 [pSK 1002] as assessed by the SOS/*umu* Test (Nakajima et al. 2006).

3.4 TOXICOKINETICS

Data on the toxicokinetics of 2-hexanone, as described in this section, were derived from studies using 2-hexanone with purity of ≥97%. As discussed below, absorption of this compound has been demonstrated in humans, dogs, and rats after administration via inhalation, oral, or dermal exposure. Very little information is available on distribution. A metabolic pathway has been proposed based on the metabolites of 2-hexanone identified in the blood of guinea pigs and rats after intraperitoneal and oral administration, respectively. Expired breath and urine appear to be the main routes of excretion for 2-hexanone and its metabolites in both animals and humans.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

The available data indicate that 2-hexanone is well absorbed after administration via the inhalation route. An analysis of the expired breath of humans who inhaled 2-hexanone at 10 or 50 ppm for 7.5 hours or 100 ppm for 4 hours indicated that 75–92% of the inhaled 2-hexanone vapor was absorbed by the lungs and respiratory tract (DiVincenzo et al. 1978).

Similarly, beagles that inhaled 2-hexanone at 50 or 100 ppm for 6 hours absorbed 65–68% of the inhaled vapor (DiVincenzo et al. 1978). More recently, whole-body exposure of rats to 75, 150, or 300 ppm 2-hexanone for 4 hours resulted in exposure-related amounts of the parent compound and the metabolites, 2-hexanol and 2,5-hexanedione, in plasma immediately after the last exposure (Duguay and Plaa 1995). At 75 and 150 ppm, the concentration of 2,5-hexanedione in plasma was approximately 5 times that of 2-hexanone; at 300 ppm, it was about 2.5 times. It should be mentioned that in rats from the mid- and high-exposure groups, the concentration of 2,5-hexanedione in plasma was significantly higher following inhalation exposure than following oral exposure (see below).

3.4.1.2 Oral Exposure

2-Hexanone also appears to be well absorbed after oral administration. Humans who ingested a single capsule containing ^{14}C-2-hexanone at 0.1 mg/kg excreted about 40% of the ^{14}C in breath and 26% in urine during the next 8 days (DiVincenzo et al. 1978). This indicates that the absorbed amount averaged at least 66% of the administered dose.

Administration of 1-^{14}C-2-hexanone at 20 or 200 mg/kg by gavage to rats resulted in excretion of about 1.2% of the administered radioactivity in the feces, about 44% in the breath, 38% in urine, and 16% remaining in the carcass (DiVincenzo et al. 1977). The results were similar at either dosage level. These findings suggest that about 98% of the administered dose was absorbed and that absorption was not saturable at the range of doses administered. Similar results were reported in rats administered three gavage doses of 50, 100, or 200 mg/kg 2-hexanone (Duguay and Plaa 1995). Plasma samples analyzed 1 hour after administration of the last dose showed dose-related amounts of 2-hexanone.

3.4.1.3 Dermal Exposure

2-Hexanone is also absorbed after dermal application. The excretion of ^{14}C in the breath and urine of two volunteers was measured after a 60-minute occlusive application of ^{14}C-2-hexanone to shaved forearms (DiVincenzo et al. 1978). Calculated skin absorption rates were 4.8 and 8.0 pg/minute/cm^2; however, the fraction of 2-hexanone that was absorbed was not calculated. ^{14}C-Hexanone was also applied to the clipped thorax of beagle dogs, and absorption was observed to be slow at first but increased dramatically after 20 minutes. At 60 minutes, 77 mg of 2-hexanone had penetrated the skin (DiVincenzo et al. 1978). The fraction of applied 2-hexanone that was absorbed was not calculated.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located regarding distribution in humans after inhalation exposure to 2-hexanone. 2-Hexanone and its metabolites, 2-hexanol and 2,5-hexanedione, were detected in the lungs of rats 1 hour after the last of three daily 4-hour exposures to 75, 150, or 300 ppm 2-hexanone (Duguay and Plaa 1995). Some degree of accumulation seemed to have occurred since the lungs of the mid- and high-exposure groups had 4 and 20 times more 2-hexanone, respectively, than the low-exposure group. The three compounds were also measured in the liver, but in contrast with the lung findings, the concentrations of

2-hexanone in the liver were exposure concentration-related. The lungs and liver were the only tissues examined in the Duguay and Plaa (1995) study. An additional metabolite, 5-hydroxy-2-hexanone, was detected in blood from cats following intermittent chronic exposure to 2-hexanone (O'Donoghue and Krasavage 1979). This metabolite was short-lived since it could not be detected on Mondays following 2 days exposure-free.

3.4.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to 2-hexanone.

In rats administered a single dose of ^{14}C-2-hexanone at 200 mg/kg by gavage, tissue distribution was reported to be widespread with highest counts in the liver and blood. No quantitative data were given on tissue distribution (DiVincenzo et al. 1977). An analysis of subcellular distribution of the ^{14}C label in liver, brain, and kidney tissue indicated highest counts were associated with the crude lipid fraction and protein, with some recovery in DNA, and little or none in RNA. Gavage administration of 50, 100, or 200 mg/kg 2-hexanone to rats for 3 days resulted in measurable amounts of the parent compound and its metabolites, 2-hexanol and 2,5-hexanedione, in the liver 1 hour after the last dose (Duguay and Plaa 1995). However, in contrast to the liver findings, no 2,5-hexanedione was detected in the lungs, which led the investigators to suggest that lung metabolism of 2-hexanone might contribute to plasma metabolite levels.

3.4.2.3 Dermal Exposure

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

3.4.2.4 Other Routes of Exposure

2-Hexanone was shown to distribute to the brain of mice within 15–90 minutes following intraperitoneal administration of a single dose of approximately 500 mg/kg of the compound (Granvil et al. 1994). Both of its metabolites, 2-hexanol and 2,5-hexanedione, were also found in the brain. Brain concentrations of 2-hexanone seemed to be lower than those measured in blood. 2-Hexanol was detected in the brain considerably earlier than 2,5-hexanedione. The study also showed that the concentrations of 2-hexanol in the brain at the various time intervals measured were approximately twice those found in blood, which according to the investigators, might explain the lower concentrations of 2-hexanone found in brain compared to those found in blood.

3.4.3 Metabolism

The proposed metabolic pathway for 2-hexanone, based on 2-hexanone metabolites identified in blood during intraperitoneal studies in guinea pigs (DiVincenzo et al. 1976) and oral studies in rats (DiVincenzo et al. 1977), is presented in Figure 3-3. DiVincenzo et al. (1978) hypothesized that the metabolic pathway for 2-hexanone is similar in humans and experimental animals based on increases in 2,5-hexanedione in serum following inhalation exposure and radiolabeled carbon dioxide in expired air following oral exposure. The metabolism of aliphatic ketones has generally been found to proceed via reduction to the corresponding secondary alcohol, which accounts for the formation of 2-hexanol. An alternate pathway is oxidation of the 5-methylene group to the corresponding alcohol, 5-hydroxy-2-hexanone, which may be followed by further oxidation to the diketone 2,5-hexanedione. Another possibility in the metabolism of 2-hexanone is the cyclization of 5-hydroxy2-hexanone to the corresponding dihydrofuran and oxidation to 2,5-dimethylfuran (DiVincenzo et al. 1977). However, the formation of these furan moieties may be the result of thermal dehydration and cyclization during gas chromatography (DiVincenzo et al. 1977). In addition, the gamma-valerolactone found in the urine (not shown in figure) is hypothesized to result from α-oxidation of 5-hydroxy-2-hexanone to 2-keto-5-hydroxyhexanoic acid, decarboxylation and oxidation to 4-hydroxypentanoic acid, and lactonization to gamma-valerolactone (DiVincenzo et al. 1977). The specific cytochrome P-450 isozymes involved in the metabolism of 2-hexanone have not been identified. The appearance of glucuronide and sulfate conjugates of 2-hexanone metabolites in the urine indicate that there is further metabolism; however, no additional information was identified.

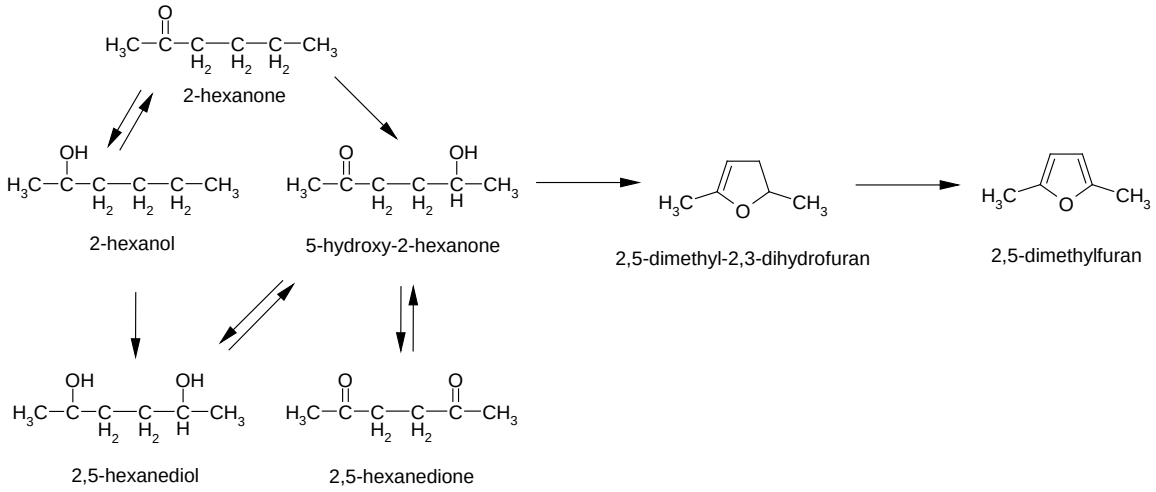
3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

In humans exposed to 2-hexanone via inhalation at 10 or 50 ppm for 7.5 hours or to 100 ppm for 4 hours, unchanged 2-hexanone (but not 2,5-hexanedione) was found in expired air during exposure, and neither 2-hexanone nor any of its metabolites was found in urine during or after exposure (DiVincenzo et al. 1978). 2-Hexanone was not detected in the expired air 3 hours after exposure to 50 or 100 ppm. These results suggest slow clearance and possible accumulation of 2-hexanone in humans exposed by this route.

In beagle dogs exposed to 2-hexanone via inhalation at 50 or 100 ppm for 6 hours, 32 and 35%, respectively, of the inhaled vapor was excreted in the expired breath (DiVincenzo et al. 1978). By 3–

Figure 3-3. Proposed Metabolic Pathway for 2-Hexanone



Source: DiVincenzo et al. 1976, 1977

5 hours after exposure, 2-hexanone was no longer detected in expired air. Excretion via other routes was not addressed.

3.4.4.2 Oral Exposure

In two humans who received a single oral dose of 1-^{14}C-2-hexanone, breath excretion of $^{14}CO_2$ reached a peak within 4 hours, then decreased slowly over the next 3–5 days. Average overall recovery of the ^{14}C-label in 8 days was 40% in breath and 26% in urine. Feces were not analyzed (DiVincenzo et al. 1978).

In rats administered a single oral dose of 1-^{14}C-2-hexanone, DiVincenzo et al. (1977) observed similar results. Radioactivity in breath accounted for about 45% of the administered dose (5% was in unchanged 2-hexanone; 40% was in $^{14}CO_2$); 35% was found in the urine; 1.5% was recovered in the feces; and about 15% remained in the carcass. In male rats that received daily gavage doses of 2-hexanone at 400 mg/kg/day for 40 weeks, very low concentrations of free 2-hexanone were detected in the urine from the third week. A maximum concentration of approximately 20 µg was reached in the 17th week (Eben et al. 1979). Similarly, free 2,5-hexanediol was found in the urine after 3 weeks and peaked in the 17th week. Free and conjugated 2,5-hexanedione was present in the urine from the 1st week of the study. The conjugated form peaked in the 7th week, whereas excretion levels of the free form were fairly consistent throughout the study. A strong correlation was observed in this study between the onset of neuropathy and the urinary concentration of 2,5-hexanedione when 2-hexanone, 2,5-hexanedione, or 2,5-hexanediol was administered orally to rats at 400 mg/kg/day.

3.4.4.3 Dermal Exposure

^{14}C from 1-^{14}C-2-hexanone applied to the forearms of two volunteers was found in the breath and urine (DiVincenzo et al. 1978). In one subject, excretion was similar by both routes; in the other subject, the levels were much higher (about 3:1) in the breath. Levels of radioactivity in feces were not measured.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of

potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. However, if the uptake and disposition of the chemical substance(s) are adequately described, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994).

PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

If PBPK models for 2-hexanone exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

PBPK models have not been developed for 2-hexanone.

3.5 MECHANISMS OF ACTION

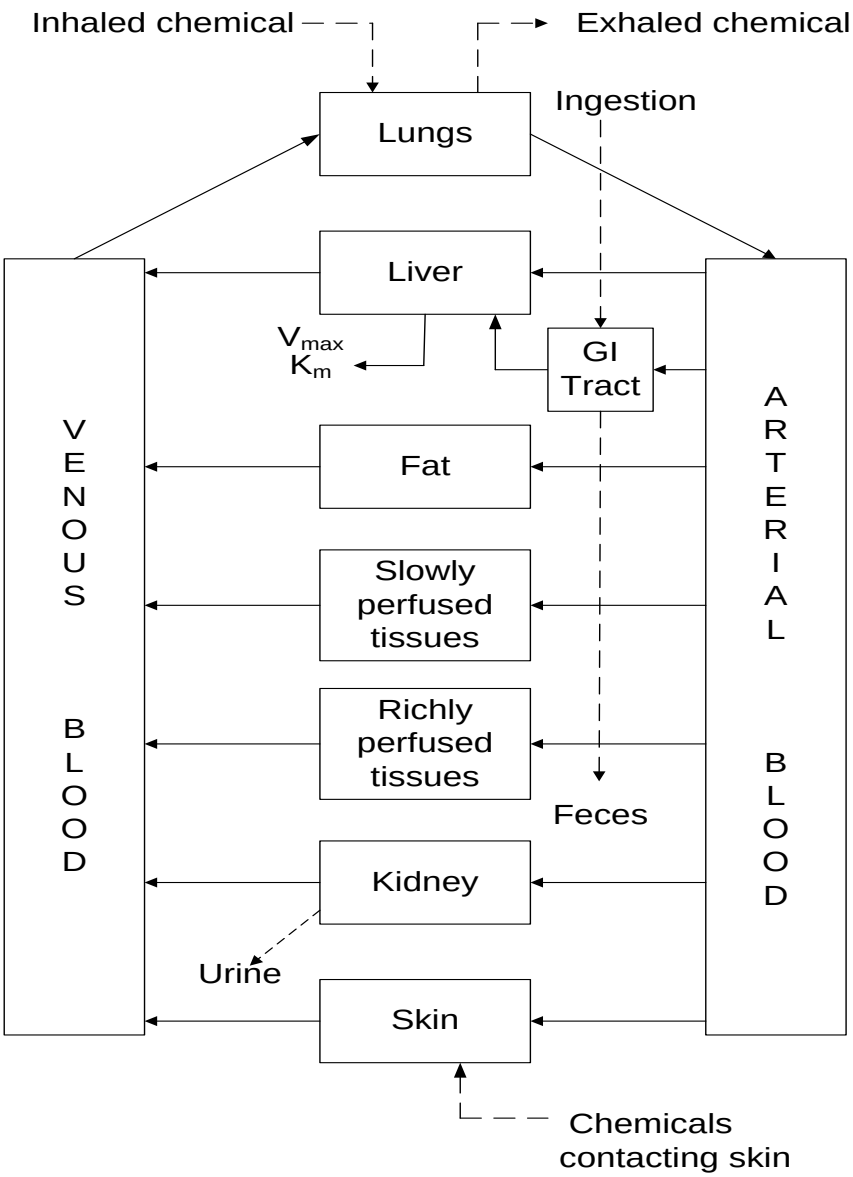
3.5.1 Pharmacokinetic Mechanisms

Absorption. No information was located regarding specific mechanisms of absorption for 2-hexanone. The chemical mixes well with oily substances and is also fairly soluble in water. Therefore, it is reasonable to assume that crossing cell membranes will be mainly by passive diffusion driven by concentration gradients.

Distribution. No information was located regarding whether there might be preferential distribution of parent compound or metabolites to specific organs or tissues. However, the fact that exposure to 2-hexanone affects principally the nervous system would suggest preferential distribution of 2,5-hexanedione, the active metabolite, to the nervous system. This appears to be due to preferential adduction of a limited number of critical lysine groups in neurofilament subunits (DeCaprio and Fowke 1992; DeCaprio et al. 1997).

Metabolism. Metabolism of 2-hexanone plays a key role in the toxicity of this chemical, as its biotransformation leads to the generation of the active metabolite, 2,5-hexanedione, responsible for the neurotoxicity of 2-hexanone. Based on the results of experiments conducted in rats, DiVincenzo et al. (1977) suggested that α-oxidation of 2-hexanone to CO_2 is a detoxification mechanism, whereas ω-1-oxidation leads to metabolic activation. Mass balance studies have not been conducted to determine how much 2,5-hexanedione is produced from a known exposure concentration/dose of 2-hexanone.

Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: Krishnan and Andersen 1994

Excretion. There is not enough information to determine whether there are exposure concentration-/dose-dependent preferential routes of excretion (i.e., urinary vs. exhaled air) for 2-hexanone and/or metabolites.

3.5.2 Mechanisms of Toxicity

As mentioned in earlier sections, the toxicity of 2-hexanone is caused by its active metabolite, 2,5-hexanedione. The mechanism of toxicity of γ-diketones has been extensively studied, not only with respect to 2-hexanone, but with a wider focus on γ-diketones in general, as this chemical is also a metabolite of other substances that induce neuropathy such as *n*-hexane. Because of the extensive nature of the literature that covers 2-hexanone, *n*-hexane, as well as 2,5-hexanedione itself, the summary below has been extracted from reviews and the reader is referred to references cited therein for more detailed information (LoPachin and DeCaprio 2004, 2005; LoPachin and Gavin 2015; LoPachin et al. 2000).

The two main features of 2-hexanone toxicity are the appearance of giant neurofilamentous axonal swellings and axonal atrophy. Results from earlier research suggested that distal swelling of myelinated fiber was the principal neuropathological manifestation of 2,5-hexanedione toxicity. Thus, the neuropathy was classified as a central-peripheral distal axonopathy. However, more recent research that combined morphological and electrophysiological techniques indicates that axonal atrophy is the most significant component of 2,5-hexanedione-induced neuropathy.

Ruling out axonal swelling as the main feature of 2-hexanone intoxication and related chemicals was based on some of the following observations. Studies showed that the *in vivo* neurotoxic potencies of various chemicals whose metabolism lead to the production of 2,5-hexanedione were correlated with the corresponding serum concentration of 2,5-hexanedione. Yet, the frequency of axonal swellings in the nerves examined did not correlate with the concentration of 2,5-hexanedione in serum. In fact, the relative frequency of swollen axons was inversely related to the serum concentration of 2,5-hexanedione and to the manifestation of neurotoxicity. This was shown to occur in both the peripheral and central nervous systems. Studies also showed that axonal swellings appeared during the later stages of 2,5-hexanedione intoxication, indicating lack of temporal association with the expression of neurological deficits. Overall, these results suggested that 2,5-hexanedione induction of neurological dysfunction was not dependent on axonal swelling and that this phenomenon could represent a secondary response to neurotoxic injury or stress.

2,5-Hexanedione-induced axonal atrophy is characterized by reduction in axon cross-sectional area without a significant change in perimeter length and degree of myelination. Morphological evaluations have shown that axon atrophy is associated with faster anterograde slow axonal transport in both peripheral nerves and in white central matter tracts of rats exposed to 2,5-hexanedione, which would lead to proximal axon atrophy and secondary distal accumulation of neurofilaments and swelling. However, subsequent studies that conducted spatio-temporal analyses showed that atrophy was widespread in the central and peripheral nervous systems and that it developed as an early consequence of 2,5-hexanedione intoxication. Observations that reductions in axon perimeter can develop in the absence of axonal swelling supported the view that axonal atrophy is the principal lesion that develops as an early consequence of 2,5-hexanedione intoxication regardless the dose or route of exposure. Further support for axonal atrophy being the main neuropathological feature of 2,5-hexanedione intoxication is the fact that reduced axon diameter is associated with reduced nerve conduction velocity.

The mechanism by which 2,5-hexanedione induces axonal atrophy has not been completely elucidated; however, studies have shown that adduction with cytoskeletal proteins plays a key role. 2,5-Hexanedione, a diketone electrophile, reacts covalently with nucleophilic lysine ε-amino groups to form 2,5-dimethylpyrrole adducts on neurofilaments and other proteins. This is thought to interfere with turnover and maintenance of the axonal cytoskeleton, and some suggested that, following formation, pyrrole adducts undergo oxidative reactions that yield cross-linked neurofilament proteins. However, since virtually all proteins, neuronal and non-neuronal, contain one or more lysine ε-amino groups, *in vivo* exposure to 2,5-hexanedione would result in multiple physiological systems being affected; however, this does not seem to be the case. In addition, *in vitro* and *in vivo* studies showed that only a very small fraction of the total available lysyl ε-amino groups on neurofilament proteins were converted to pyrrole adducts, so a specific mechanism needed to be involved. Further *in vitro* experiments showed that the adducted lysine residues were primarily located within the KSP (lysine-serine-proline) repeat on the C-terminal regions of neurofilament-M and neurofilament-H subunit proteins.

Exactly how neurofilament protein adduction can lead to axonal atrophy is not totally understood. Results from some studies suggested that 2,5-hexanedione might reduce phosphorylation of neurofilaments, an important determinant of cytoskeletal protein turnover and axon diameter. Reduced phosphorylation would prevent neurofilaments from associating with the cytoskeletal polymer or cause premature dissociation of integrated neurofilaments. In turn, depletion of neurofilaments by anterograde transport of hypophosphorylated neurofilaments would lead to loss of axon diameter. More recent data have shown that 2,5-hexanedione can affect components of the axon cytoskeleton other than

neurofilament subunit proteins. Studies in rats treated orally with 2,5-hexanedione showed that 2,5-hexanedione impaired binding of microtubule associated proteins (e.g., MAP1A, tau) to recognition sites on microtubules. Presumably, this disruption was caused by 2,5-hexanedione adduct formation with ε-amino groups on lysine residues that mediate such protein-protein interactions. Based on the critical role in cytoskeletal physiology, MAPs could represent a relevant target of γ-diketone axonopathy. Studies also suggested that higher molecular weight neurofilament derivatives were not a consequence of 2,5-hexanedione cross-linking of these proteins, because they also appeared in nervous tissues of untreated animals. Rather, these derivatized neurofilaments likely represented baseline levels of proteins that were cross-linked by normal activities of axon transglutaminases that increase cytoskeletal stability. The elevated content of higher molecular weight neurofilament complexes in 2,5-hexanedione-treated rats was thought to represent excess fragmentation of the stationary cytoskeleton possibly as a result of 2,5-hexanedione-impaired polymer maintenance.

3.5.3 Animal-to-Human Extrapolations

2-Hexanone, via its metabolite, 2,5-hexanedione, affects mainly the nervous system (Abdel-Rahman et al. 1978; DiVincenzo et al. 1976, 1978; Eben et al. 1979). Most animal species tested have shown similar clinical signs and morphological alterations in the peripheral nervous system, as have humans exposed to 2-hexanone itself or to *n*-hexane, a chemical that is also biotransformed into 2,5-hexanedione. Comparative studies have shown the relative species sensitivity to 2-hexanone as chicken > cat > dog > primate > rat (Abdo et al. 1982; Mendell et al. 1974b). While many studies have been conducted in hens/ chickens and are useful for hazard identification, they are not useful for risk assessment. As mentioned earlier, because their digestive and respiratory systems are different from mammals, it is not known whether the dose-response in this species is applicable to humans.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a

panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans or animals after exposure to 2-hexanone. Available inhalation and oral studies that have examined endocrine glands in animals have not reported gross or microscopic alterations in the glands following exposure to 2-hexanone (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979; O'Donoghue et al. 1978). However, endocrine end points have not been examined in detail.

No *in vitro* studies were located regarding endocrine disruption of 2-hexanone.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when most biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect

effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to adverse health effects from exposure to hazardous chemicals, but whether there is a difference depends on the chemical(s) (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to exposure-related health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life that are most sensitive to disruption from exposure to hazardous substances. Damage from exposure in one stage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). Past literature has often described the fetus/infant as having an immature (developing) blood-brain barrier that is leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the brain, there are differences between fetuses/infants and adults that are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult.

Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; whether these mechanisms provide protection for the developing brain or render it more vulnerable to toxic injury is an important toxicological question. Chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns given their low glomerular filtration rate and not having developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There are no studies of humans that could help determine whether children are more susceptible than adults to the effects of exposure to 2-hexanone. Likewise, there are no studies in animals that examined the comparative sensitivity of young and older animals to 2-hexanone.

To the extent that the metabolism of 2-hexanone involves cytochrome P-450 enzymes, some of which are known to be developmentally regulated, infants may be at higher or lower risk of 2-hexanone toxicity depending on whether oxidative (activation) or reductive (detoxification) reactions prevail in the initial steps of 2-hexanone metabolism.

3.8 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 (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, 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 2-hexanone are discussed in Section 3.8.1.

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 2-hexanone are discussed in Section 3.8.2.

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 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to 2-Hexanone

2-Hexanone and its various metabolic products (2-hexanol, 2,5-hexanedione, 5-hydroxy-2-hexanone, 2,5-dimethylfuran) can be measured in biological tissue, fluid, and excreta (Fedtke and Bolt 1986; Nomeir and Abou-Donia 1985; O'Donoghue and Krasavage 1979; White et al. 1979). The currently available information, however, does not indicate whether the levels of these substances can be used to calculate or estimate corresponding levels of exposure to 2-hexanone. Because exposure to other substances, for example *n*-hexane, also produce 2,5-hexanedione as a metabolite, identification of 2,5-hexanedione in the urine does not necessarily indicate that exposure to 2-hexanone occurred.

It is worth noting that 2,5-hexanedione has been identified in the urine of subjects in Italy who had not been occupationally exposed to 2-hexanone or *n*-hexane (Bavazzano et al. 1998). The investigators proposed that 2,5-hexanedione had both an endogenous and an exogenous origin. The former is related to pollution due to exposure to solvents and the latter is based on the hypothesis that 2,5-hexanedione might be an intermediate catabolite of some biochemical physiological processes. However, the study did not provide any support for an endogenous origin.

3.8.2 Biomarkers Used to Characterize Effects Caused by 2-Hexanone

There are no biomarkers specific for exposure to 2-hexanone. The main effect of exposure to 2-hexanone is neuropathy. Signs of neuropathy can be monitored by non-invasive procedures such as measurement of nerve conduction velocities, amplitude of evoked muscle action potentials, and amplitude of evoked sensory action potentials. However, these signs are not exclusive to exposure to 2-hexanone. They can occur due to exposure to other chemicals or can be caused by conditions not even associated with chemical exposures.

3.9 INTERACTIONS WITH OTHER CHEMICALS

There are limited data on the effect of other chemicals on the toxicity of 2-hexanone. A study in which rats were exposed via inhalation to a combination of 2-hexanone and methyl ethyl ketone resulted in the potentiation of severe neurotoxic effects including paralysis and histopathological changes. These effects were either not observed or they occurred at much lower frequencies when either of the two compounds was administered separately (Saida et al. 1976). Similarly, dermal or inhalation exposure in hens to 2-hexanone in combination with dermal application of the pesticide, 0-ethyl-0-4-nitrophenyl phenylphosphonothioate (EPN), has resulted in earlier onset and far more severe clinical and histological manifestations of neurotoxic effects than with either chemical exposure alone (Abou-Donia et al. 1985a, 1985b). The authors speculated that this potentiation effect may have been due to induction of hepatic microsomal cytochrome P-450 by EPN, leading to increased metabolism of 2-hexanone to its neurotoxic metabolite, 2,5-hexanedione. An alternate explanation is that local trauma to the nervous tissue produced by 2-hexanone and EPN might increase vascular permeability and thus increase the entry of these compounds and their metabolites from circulation.

Given that 2-hexanone and n-hexane have similar active metabolites, interaction studies with n-hexane provide information on potential for interactions for 2-hexanone. As discussed in the toxicological profile for n-hexane (ATSDR 1999), co-exposure of n-hexane with methyl ethyl ketone or acetone increased the neurotoxicity of n-hexane. In contrast, co-exposure of n-hexane with xylene or toluene prevented or reversed the decreased nerve conduction velocity that was associated with exposure to n-hexane only. This protective effect may have been due to metabolic competition resulting in a decrease in the metabolism of n-hexane to 2,5-hexanedione (ATSDR 1999). Although no studies were identified, it is that likely that co-exposure to 2-hexanone and n-hexane would result in additive or greater-than-additive toxicity. Additionally, co-exposure to other compounds that have similar mechanisms of neurotoxicity or result in alterations that favor the production of 2,5-hexanedione (e.g., methyl isobutyl ketone) may influence the toxicity of 2-hexanone.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 2-hexanone than will most persons exposed to the same level of 2-hexanone in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of 2-hexanone, or compromised function of organs affected by 2-hexanone. Populations who are at greater

risk due to their unusually high exposure to 2-hexanone are discussed in Section 6.7, Populations with Potentially High Exposures.

No specific population has been identified that is unusually susceptible to toxic effects resulting from exposure to 2-hexanone.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 2-hexanone. Because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 2-hexanone. When specific exposures have occurred, poison control centers, board certified medical toxicologists, board-certified occupational medicine physicians and/or other medical specialists with expertise and experience treating patients overexposed to 2-hexanone can be consulted for medical advice. The following texts provide specific information about treatment following exposures to 2-hexanone:

Gummin DD. 2015. Hydrocarbons. In: Hoffman RS, Lewin NA, Goldfrank LR, et al., eds. Goldfrank's toxicologic emergencies. 10th ed. New York, NY: McGraw-Hill Education, 1334-1345.

Additional relevant information can be found in the front section of this profile under QUICK REFERENCE FOR HEALTH CARE PROVIDERS.

3.11.1 Reducing Peak Absorption Following Exposure

Gummin (2015) indicates the following:

> "Exposed clothing should be removed and safely discarded as further absorption or inhalation of hydrocarbons from grossly contaminated clothing can worsen systemic toxicity. Decontamination of the skin should have a high priority in massive hydrocarbon exposures, particularly those exposures involving highly toxic hydrocarbons. Water alone may be ineffective in decontaminating most hydrocarbons, but early decontamination with soap and water may be adequate.
>
> Several studies have attempted to evaluate the role of gastric decontamination after hydrocarbon ingestion. Results were largely inconclusive and the level of evidence, poor. In the subset of patients who were randomized to receive gastric lavage, 44% had pulmonary complications, compared with 47% of those who were not lavaged. Although available studies do not offer a conclusive answer to the question of gastric emptying after hydrocarbon ingestion, the high incidence of spontaneous emesis and the risk of aspiration essentially eliminate any consideration of gastric emptying in all but the rarest of cases."

3.11.2 Reducing Body Burden

According to Gummin (2015):

> "Activated charcoal (AC) has limited ability to decrease gastrointestinal absorption of hydrocarbons and may distend the stomach and predispose patients to vomiting and aspiration. The use of AC may be justified in patients with mixed overdoses, but its role in isolated hydrocarbon ingestions appears very limited."

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Studies have shown that 2-hexanedione, the toxic metabolite of 2-hexanone, disrupts neurofilament subunit structure by forming adducts with soluble neurofilament protein, resulting in reduced axon caliber and eventually axonal atrophy (see reviews by LoPachin and DeCaprio [2004, 2005] and LoPachin et al. [2005a, 2005b]). There are no established methods to interfere with any of the multiple biochemical steps that occur between the formation of the active 2,5-hexanedione and ultimately axonal atrophy.

3.12 ADEQUACY OF THE DATABASE

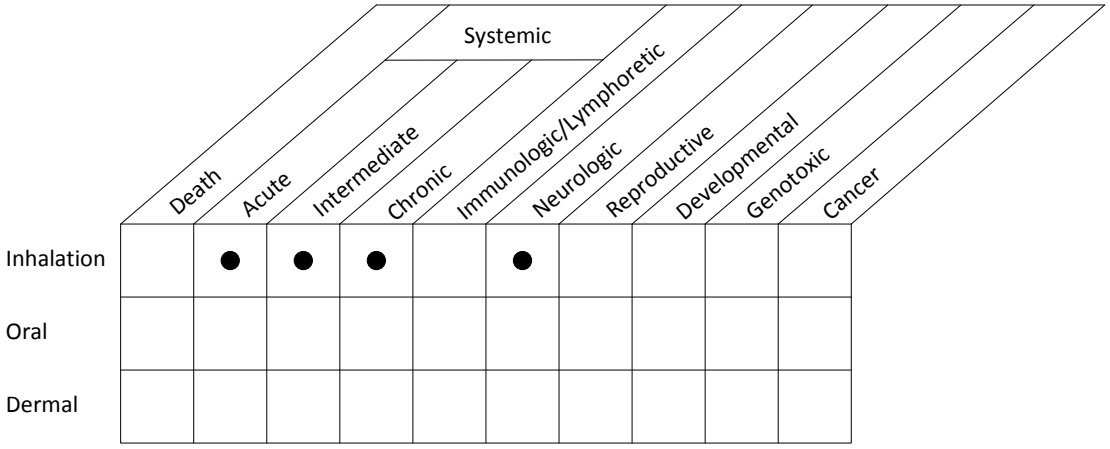
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 2-hexanone is available. Where adequate information is not 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 adverse health effects (and techniques for developing methods to determine such health effects) of 2-hexanone.

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 risk 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.

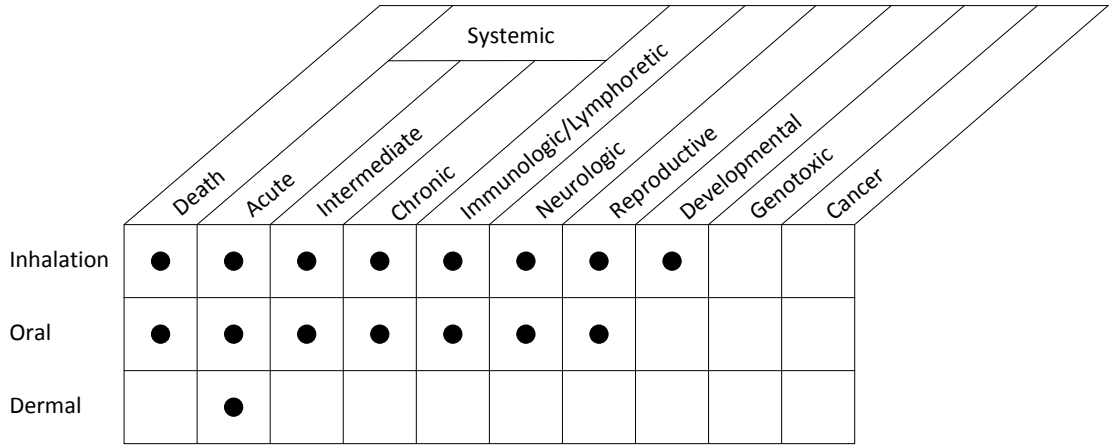
3.12.1 Existing Information on Health Effects of 2-Hexanone

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 2-hexanone are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing

Figure 3-5. Existing Information on Health Effects of 2-Hexanone



Human



Animal

● Existing Studies

information concerning the health effects of 2-hexanone. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 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.

Data regarding health effects of 2-hexanone in humans come essentially from two reports of workers exposed to the chemical primarily by inhalation, although oral and dermal exposure may have also occurred. These reports provide information on systemic and neurological effects; the latter are the main effects induced by 2-hexanone in humans and animals. Inhalation and oral studies in animals are available. These studies provide information mainly on systemic and neurological effects. Limited data are available regarding immunological, reproductive, and developmental effects of 2-hexanone, and no cancer data are available in humans or animals. Interpretation of many animal studies is problematic because the studies did not state the purity of the 2-hexanone used. Purity of commercial grade 2-hexanone can be as low as 70% with the remainder predominantly MiBK, which has been shown to potentiate the toxicity of 2-hexanone.

It is unlikely that many persons are currently occupationally exposed to 2-hexanone, other than as a degradation product resulting from wood pulping, *in situ* oil shale processing, or coal gasification operations. The general population could be exposed orally or through contact with the skin if leakage from waste sites contaminate water sources or soil. It is possible that exposure to small amounts of 2-hexanone may occur through imported products containing 2-hexanone, such as foods, and from consumer products manufactured prior to 1982, such as lacquers, primers, sealers, and thinners, that contain 2-hexanone.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. The only data available on humans for this exposure duration is that exposure to concentrations ≥2,300 ppm 2-hexanone in the air caused irritation of the eyes and nasal passages in men (Schrenk et al. 1936). In addition, there is no information on acute toxicity in animals

following dermal exposure. Acute inhalation exposure to ≥2,300 ppm caused nose and eye irritation in guinea pigs (Schrenk et al. 1936). Acute lethality data are available for guinea pigs via inhalation exposure (Schrenk et al. 1936) and for rats via the oral route (Smyth et al. 1954). Neither an acute-duration inhalation nor oral MRL could be derived due to lack of adequate studies. The existing data are insufficient to derive an MRL for any route of exposure. Acute-duration studies would be useful for determining minimal doses and exposure durations that can induce neurological effects in short-term studies.

Intermediate-Duration Exposure. The currently available data on humans exposed to 2-hexanone for this duration period is based on a study of workers exposed to 2-hexanone for ≥5 weeks (Allen et al. 1975; Billmaier et al. 1974). Peripheral neuropathy and weight loss were the major observations. Several limitations including exposure to other chemicals and possibly significant oral and dermal exposure precluded using this study for derivation of an intermediate-duration inhalation MRL. Repeated-dose studies in rats, cats, monkeys, and guinea pigs indicate that the nervous system is the primary target of 2-hexanone exposure via inhalation (Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Mendell et al. 1974b; Saida et al. 1976; Spencer et al. 1975) or orally (Abdel-Rahman et al. 1978; Eben et al. 1979; Krasavage et al. 1980; Union Carbide 1977) for this duration. Most intermediate-duration studies tested only one exposure concentration or dose level and many did not provide information regarding the purity of the test material. Because the lowest exposure levels tested were serious LOAELs for neurological effects, no intermediate-duration MRLs were derived. A 90-day study with pure 2-hexanone that examines multiple end points would be valuable for establishing dose-response relationships. Such a study could be conducted in animals exposed orally since oral exposure may occur via contaminated water or soil near waste sites.

Chronic-Duration Exposure and Cancer. Some of the workers exposed to 2-hexanone that developed peripheral neuropathy studied by Allen et al. (1975) had been exposed to the chemical for chronic durations. No additional chronic-duration studies in humans were located. As mentioned above, however, confounders in the Allen et al. (1975) study precluded its use for MRL derivation. There are two chronic-duration inhalation studies in animals, one in rats (Krasavage and O'Donoghue 1977) and the other in cats (O'Donoghue and Krasavage 1979). Both studies examined multiple end points and the lowest exposure concentration tested, 100 ppm, was a NOAEL for neurological effects. Because the exposure level of 100 ppm was a serious LOAEL for neurological effects in intermediate-duration studies, a chronic-duration inhalation MRL for 2-hexanone could not be derived based on the studies by Krasavage and O'Donoghue (1977) and O'Donoghue and Krasavage (1979). There is one chronic-

duration oral study available in rats exposed to pure 2-hexanone that examined multiple end points (O'Donoghue et al. 1978); this study was used to derive a chronic-duration oral provisional MRL for 2-hexanone. Additional chronic studies do not seem necessary at this time.

There are no studies of cancer in humans exposed to 2-hexanone. The few chronic-duration studies available (Krasavage and O'Donoghue 1977; O'Donoghue et al. 1978; O'Donoghue and Krasavage 1979) have focused mainly on neurological effects, but have also examined multiple tissues and organs and have not reported treatment-related increases in tumors. It seems that chronic cancer bioassays for 2-hexanone are not necessary at this time.

Genotoxicity. Only one genotoxicity study of 2-hexanone was located. That study reported that 2-hexanone was mutagenic in *S. typhimurium* 1535 [pSK 1002] as assessed by the SOS/*umu* Test (Nakajima et al. 2006). A battery of *in vitro* genotoxicity tests with 2-hexanone would be useful as a preliminary step in assessing its mutagenic potential and determining if further genotoxicity tests are warranted.

Reproductive Toxicity. There is no information on the effects of 2-hexanone on reproductive parameters in exposed humans via any route of exposure. Limited studies in animals have not produced conclusive results. Reduced testes weight and induced atrophy of the testicular germinal epithelium of male rats were reported in an intermediate-duration inhalation study (Katz et al. 1980); however, chronic exposure of male rats and female cats to ≤330 ppm 2-hexanone of unreported purity did not induce gross or microscopic alterations in the reproductive organs of either species (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979). In oral studies, 2-hexanone induced testicular toxicity in male rats when given by gavage (Krasavage et al. 1980), but not when given in the drinking water to male rats (O'Donoghue et al. 1978) in comparable doses. Exposure to 2,5-hexanedione can result in testicular damage (increased spermatid heads) in rats (Bryant et al. 2008). None of the available 2-hexanone studies assessed fertility. A 2-generation reproductive toxicity study could provide useful data.

Developmental Toxicity. There is no information on the effects of exposure to 2-hexanone via any route on human development. There are no animal studies using the oral or dermal routes. The currently available data for animals is based on a single inhalation study in pregnant rats in which relatively high 2-hexanone exposure resulted in decreased litter size and pup weight and in behavioral effects in the offspring tested later in life (Peters et al. 1981). Additional studies would be useful to confirm or refute the findings of Peters et al. (1981).

Immunotoxicity. There are currently no data on the effects of 2-hexanone on the human immune system via any route of exposure. 2-Hexanone did not induce morphological alterations in lymphoreticular organs or tissues of rats or cats in long-term inhalation or oral studies (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979; O'Donoghue et al. 1978; Union Carbide 1977). However, none of these studies examined parameters of immunocompetence. A screening (Tier I) study using a battery of tests (immunopathology, humoral- and cell-mediated immunity, nonspecific immunity) (Luster et al. 1988) would provide valuable results.

Neurotoxicity. The nervous system has been clearly established as the major target for 2-hexanone in humans exposed via inhalation (Allen et al. 1975; Billmaier et al. 1974) and in animals exposed via any route of exposure (Abdel-Rahman et al. 1978; Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Krasavage et al. 1980; Krasavage and O'Donoghue 1977; O'Donoghue et al. 1978; O'Donoghue and Krasavage 1979; Saida et al. 1976; Spencer et al. 1975; Union Carbide 1977). However, most of the available information is derived from studies using 2-hexanone of low or unknown purity or using it at a single dosage level, so its usefulness is limited. Animal data that would clearly establish dose-response relationships for neurological effects, including histopathological damage as well as clinical manifestations, as a result of exposure to pure 2-hexanone via all routes of exposure and using a range of exposure durations would be useful. This information would be valuable in assessing the potential risks of neurotoxicity in persons exposed to 2-hexanone in the vicinity of hazardous waste sites. In addition, continued research aimed at determining the mode of action of 2,5-hexanedione, the active neurotoxic metabolite at the molecular level would be valuable.

Epidemiological and Human Dosimetry Studies. The only epidemiological information that is currently available is the study of workers in a plant producing plastic-coated and color-printed fabrics (Allen et al. 1975; Billmaier et al. 1974). Some workers developed peripheral neuropathy whose origin was traced to exposure to 2-hexanone, although exposure to other chemicals also occurred. Because 2-hexanone is no longer manufactured or used commercially in the United States, it is unlikely that many persons are currently occupationally exposed to 2-hexanone, other than as a degradation product resulting from wood pulping, *in situ* oil shale processing, or coal gasification operations. Identification and evaluation of populations having long-term exposure to 2-hexanone due to, for example, contamination of drinking water, for neurological, reproductive, developmental, and cancer effects would be useful.

Biomarkers of Exposure and Effect.

Exposure. Measurement of 2-hexanone and its metabolites in blood or urine may not provide an adequate indication of exposure to this substance, since these metabolites may also result from exposure to *n*-hexane (Fedtke and Bolt 1986; Nomeir and Abou-Donia 1985; White et al. 1979). Further work in the characterization of the neurofilament protein adduct produced by the active metabolite, 2,5-hexanedione would be useful.

Effect. The major target organ of 2-hexanone in humans is the nervous system (Allen et al. 1975), and morphological effects may occur before clinical manifestations of toxicity (Egan et al. 1980). Development of non-invasive imaging procedures that can identify morphological alterations in peripheral nerves and in central tracts would be useful.

Absorption, Distribution, Metabolism, and Excretion. Although some information is available on each of these topics from studies conducted in several species, more information in each of these areas would be useful. In addition, because most of these studies were conducted by the same group of researchers, further studies in other laboratories in each of these areas would be useful in confirming the available data.

Available data indicate that 2-hexanone is readily absorbed by humans and various animal species after inhalation, oral, or dermal administration (DiVincenzo et al. 1977, 1978). Estimates are available regarding the rates of absorption via the inhalation and oral routes in humans (DiVincenzo et al. 1978), but information is lacking regarding rates of dermal absorption. Also lacking is information regarding possible mechanism(s) by which 2-hexanone is absorbed through the lungs, gastrointestinal tract, and skin.

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Limited information on distribution of 2-hexanone is available. An inhalation study in rats reported distribution of 2-hexanone and metabolites to the lungs and liver but did not examine any other organ or tissue (Duguay and Plaa 1995). It also appeared that some accumulation occurred in the lungs at exposure concentrations ≥150 ppm. Further studies, particularly longer-term studies that examine potential distribution to additional tissues, especially the nervous system would be valuable. An environmentally relevant route of exposure (i.e., oral, dermal) is preferred over parenteral dosing.

The proposed metabolic pathway for 2-hexanone is based on blood metabolites identified during intraperitoneal studies in guinea pigs (DiVincenzo et al. 1976) and oral studies in rats (DiVincenzo et al. 1977). The metabolite, 2,5-hexanedione, has also been found in human serum after inhalation exposure (DiVincenzo et al. 1978). Because studies in rats exposed to 2-hexanone have indicated a strong relationship between the concentration of 2,5-hexanedione in the urine and the onset of neuropathic signs (Eben et al. 1979), it would be useful to also have this information for humans.

Limited excretion data are available in humans receiving 2-hexanone via inhalation, oral, and dermal exposure, in dogs via inhalation exposure, and in rats via oral exposure (DiVincenzo et al. 1977, 1978). However, human data on excretion of 2-hexanone via feces are not available, and the available information in dogs concerns excretion via exhaled breath only. In these and any other studies, information on all routes of excretion would help to evaluate the potential for 2-hexanone clearance in the exposed species. Excretion data in rats receiving 2-hexanone via inhalation and dermal application and in other species receiving 2-hexanone via all three routes would be useful for comparison with the human data and to assess the comparative risks of exposure by each route. In addition, information on excretion rates in each species via each route would be helpful in understanding how long 2-hexanone and its metabolites may persist in the body.

Comparative Toxicokinetics. The toxicokinetic studies available in both humans and animals (dogs, rats, and guinea pigs) suggest that there may not be any major differences in the kinetics of this compound across certain species. Metabolites of 2-hexanone in the expired breath (carbon dioxide) of humans and rats exposed via the oral route and the presence of 2,5-hexanedione in the serum of humans exposed via inhalation, as well as in the blood and urine of orally exposed rats and the intraperitoneally exposed guinea pigs, suggest that there is a similar metabolic pathway in humans and experimental animals (DiVincenzo et al. 1976, 1977, 1978). Confirmation of this assumption would be useful. Similar toxic effects, neuropathy and weight loss, have been noted in several species (humans, monkeys, rats, cats, hens, and guinea pigs) (Abdel-Rahman et al. 1978; Allen et al. 1975; Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Krasavage et al. 1980; O'Donoghue et al. 1978; Saida et al. 1976; Spencer et al. 1975). Therefore, it would also be useful to investigate patterns of distribution, to identify target organs, and to measure rates of excretion in several species and to identify blood metabolites in humans in order to investigate interspecies similarities and differences. Studies in this area would be valuable for predicting toxic effects in humans and for studying the mechanisms of action of this chemical.

Methods for Reducing Toxic Effects. As previously mentioned, there are no established methods to interfere with any of the multiple biochemical steps that occur between the formation of the active toxic metabolite of 2-hexanone, 2,5-hexanedione, and ultimately axonal atrophy. Further research in this area is needed.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There are no studies of children exposed to 2-hexanone or animal studies that compare the susceptibility of animals of various ages to 2-hexanone. Any research in this area could provide valuable information.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

No relevant ongoing research regarding 2-hexanone was identified in the National Institute of Health (NIH) RePORTER (2016) database.

4. CHEMICAL AND PHYSICAL INFORMATION

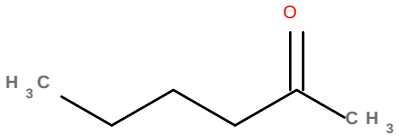
4.1 CHEMICAL IDENTITY

Table 4-1 lists common synonyms, trade names, and other pertinent identification information for 2-hexanone.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 4-2 lists important physical and chemical properties of 2-hexanone.

Table 4-1. Chemical Identity of 2-Hexanone[a]

Characteristic	Information
Chemical name	2-Hexanone
Synonym(s)	Methyl *n*-butyl ketone; MBK; 2-oxohexane; *n*-butyl methyl ketone, propylacetone; MnBK
Registered trade name(s)	No data
Chemical formula	$C_6H_{12}O$
Chemical structure	
Identification numbers:	
CAS registry	591-78-6
NIOSH RTECS	MP1400000[b]
EPA hazardous waste	No data
DOT/UN/NA/IMDG shipping	1224[b]
HSDB	543
NCI	No data

[a]All information obtained from HSDB (2009), unless otherwise noted.
[b]NIOSH 2015

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = 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; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of 2-Hexanone

Property	Information
Molecular weight	100.16
Color	Colorless
Physical state	Liquid
Melting point	-55.5°C
Boiling point	127.2°C
Density:	
at 20°C/20°C	0.83
Odor	Similar to acetone, but more pungent
Odor threshold:	
Water	0.25 mg/L
Air	0.076 ppm (0.31 mg/m^3)
Taste threshold	No data
Solubility:	
Water at 20°C	1.72x10^4 mg/L
Organic solvent(s)	Soluble in acetone; miscible in ethanol and ether
Partition coefficients:	
Log K_{ow}	1.38
Log K_{oc}	No data
Vapor pressure	
at 25°C	11.6 mm Hg
Henry's law constant	9.32x10^{-5} atm-m^3/mol at 25°C (estimated)
Autoignition temperature	795°F (423°C)
Flashpoint	95°F (35°C) (open cup); 77°F (25°C) (closed cup)
Flammability limits	1.2–8%
Conversion factors at 25°C, 760 mm Hg	1 ppm=4.10 mg/m^3 1 mg/L=244 ppm
Explosive limits	1.22–8%

Source: HSDB 2009.

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

5.1 PRODUCTION

No information is available in the TRI database on facilities that manufacture or process 2-hexanone because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005).

In 1977, the combined U.S. production and import of 2-hexanone was between 453 and 4,500 metric tons (EPA 1981, 1987); no breakdown of these figures was provided. The only U.S. producer of 2-hexanone, the Tennessee Eastman Company division of Eastman Kodak, discontinued its production of 2-hexanone in 1979 and sold its remaining reserves by 1981 (EPA 1981, 1987; Lande et al. 1976). 2-Hexanone was commercially produced by the catalyzed reaction of acetic acid and ethylene under pressure (EPA 1987). 2-Hexanone may still commercially produced in countries outside of the United States.

5.2 IMPORT/EXPORT

Currently, 2-hexanone is not produced or approved for commercial use in the United States, and consequently, there is no information on exports or imports (DHHS 2017; EPA 1987).

5.3 USE

2-Hexanone is not currently manufactured, processed, or used for commercial purposes in the United States (DHHS 2017; EPA 1987). 2-Hexanone had been used as a solvent for many materials, primarily in the lacquer industry as a solvent for lacquers and varnish removers. It had also been used as a solvent for ink thinners, resins, oils, fats, and waxes, and as a medium evaporating solvent for alkyd, vinyl, and nitrocellulose acrylate coatings. 2-Hexanone had also been used as an intermediate in the synthesis of organic chemicals (ACGIH 1986; EPA 2009a). 2-Hexanone has been studied as a possible oxygenate in blended diesel fuels; however, it absorbs water and is susceptible to gum formation (McCormick et al. 2015).

5.4 DISPOSAL

No data were located regarding the disposal of 2-hexanone or on regulations and guidelines regarding its disposal. The favored method for disposal of ketones is incineration (Lande et al. 1976).

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6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

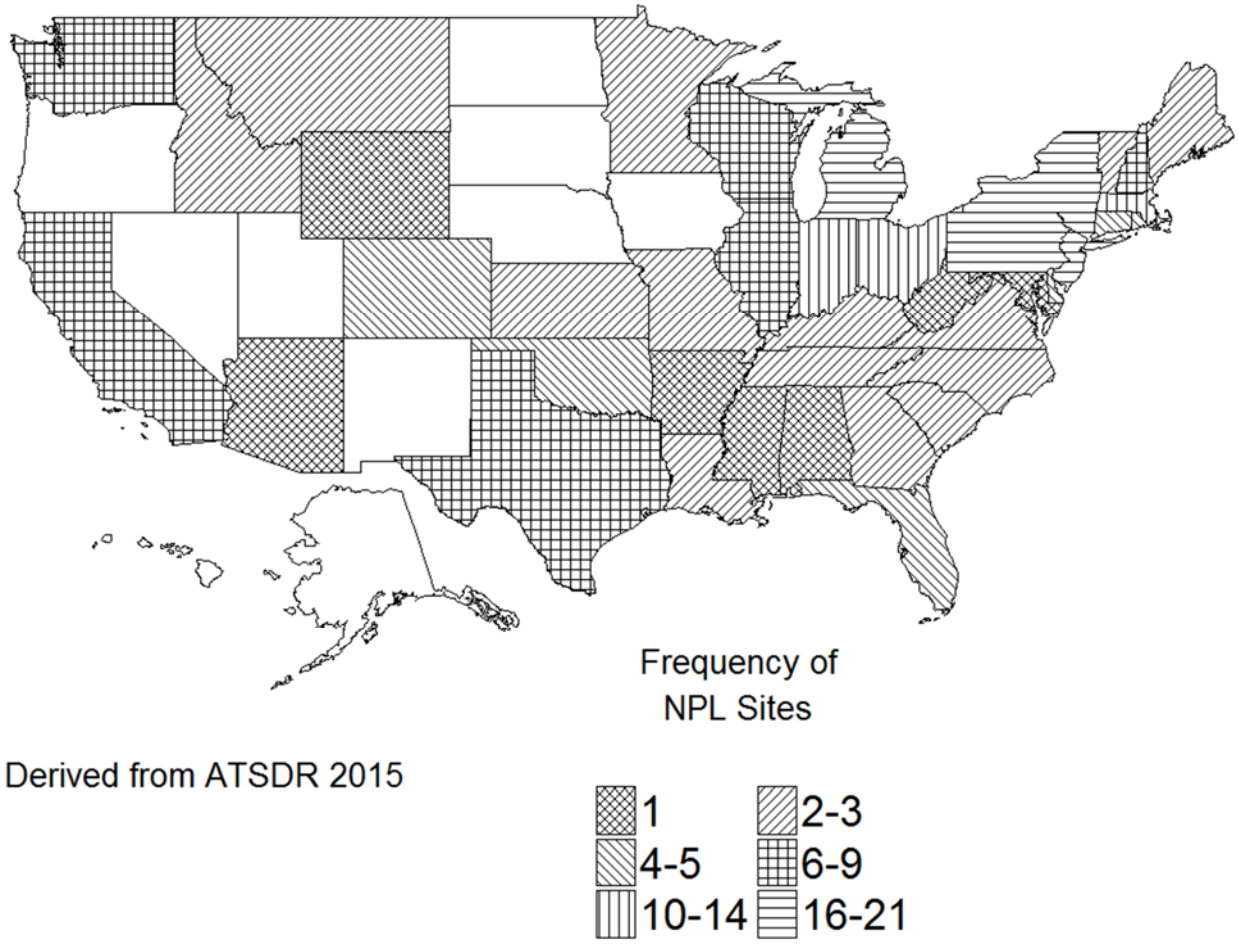
2-Hexanone has been identified in at least 224 of the 1,832 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2015). However, the number of sites in which 2-hexanone has been evaluated is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 221 are located within the United States and 1 and 2 are located in Guam and the Commonwealth of Puerto Rico (not shown), respectively.

2-Hexanone is a volatile organic liquid that is very soluble in water. It is expected to be quite mobile in water and soils. Its rate of volatilization is likely to be moderately fast, but equilibration with sediments will be low. Biodegradation of 2-hexanone may occur slowly in water and soil, but bioconcentration is not expected.

2-Hexanone has been identified in aqueous streams and air samples associated with the oil and natural gas industries (ATSDR 2008; Grinberg 2014; Pellizzarri et al. 1979). 2-Hexanone is formed as a degradation product of 2-hexanol, which is a biodegradation product of n-hexane (ATSDR 1999; Lee et al. 2010), which is contained in fossil fuels. It may also be released to the environment as a component of hydroprocessed plant biomass pyrolysis oils (McCormick et al 2015). 2-Hexanone has also been detected in groundwater at several hazardous waste sites (Canter and Sabatini 1994; Plumb 1992). Since 2-hexanone is no longer used commercially in the United States, exposure to the general population is expected to be low. However, some populations residing near hazardous waste sites or gas- and oil-related activities may be exposed to low levels of 2-hexanone.

2-Hexanone is an oxidation product of fatty acids by ketone-forming molds, and exposure to small amounts of 2-hexanone may occur by ingestion of foods in which it has been detected (Dumont and Adda 1978; Girolami and Knight 1955). However, these levels are far below the levels that have caused harmful effects in animals. In the past, occupational exposures to 2-hexanone resulted from its manufacture and use. However, since 2-hexanone is not currently manufactured or used commercially in the United States, occupational exposures related to these activities are no longer of special concern. Insufficient monitoring data are available to estimate average human daily intakes of 2-hexanone from food, inhalation, or drinking water.

Figure 6-1. Frequency of NPL Sites with 2-Hexanone



6.2 RELEASES TO THE ENVIRONMENT

Because 2-hexanone is not currently manufactured, imported, processed, or used for commercial purposes in the United States (EPA 1987), releases to the environment are not likely to be high. Although it is reported to be released from currently operating wood pulping, coal-gasification, and *in situ* oil-shale processing[1] plants via liquid waste water containing 2-hexanone or as a volatilized gas from waste water into the surrounding air, levels resulting from these operations have been reported as being low (ATSDR 2008; Pellizzari et al. 1979). In the past decade, there has been an increase in oil and natural gas production due to the development of horizontal drilling and hydraulic fracturing (EIA 2016). There is some evidence that 2-hexanone may be released from these operations; however, the data are limited.

6.2.1 Air

There is no information in the TRI on releases of 2-hexanone to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Limited studies were located regarding the amount of 2-hexanone released to the atmosphere. 2-Hexanone was detected at a maximum average concentration of 1,700 µg/m^3 in the air emissions of eight municipal solid waste composting disposal facilities in the United States (Eitzer 1995). Kumar et al. (2011) also reported 2-hexanone to be a volatile organic compound emission from green waste composting. Municipal solid waste composting facilities collect waste, including yard waste, food scraps, farm waste, cardboard, newspaper, and sewage treatment plant solids, from non-industrial sources such as residential homes, restaurants, retail centers, and office buildings. Therefore, the 2-hexanone detected in air emissions is likely produced from the microbial digestion of large bioorganic compounds.

2-Hexanone can be released to the air from activities involving the oil and gas industry if waste water is stored in open containment pits. For example, a report from an environmental nonprofit group reported that 2-hexanone was detected in air samples above oil and gas waste water open containment ponds located in Kern County, California at a concentration of 12 µg/m^3 (Grinberg 2014). Hawthorne and Sievers (1984) measured 2-hexanone at levels of 0.22–3.6 ng/mL in air samples above shale oil waste water retort water and gas condensate. Since 2-hexanone is no longer produced in the United States (EPA 1987b) or used commercially (EPA 1987b; Lande et al. 1976; O'Donoghue 1985), atmospheric emissions from industrial sources are likely to be small.

[1] *In situ* shale oil processing involves drilling into oil shale strata and heating rocks to release crude shale oil, shale gas, and water (referred to as termed retorting).

6.2.2 Water

There is no information on releases of 2-hexanone to the water from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

2-Hexanone may be released to water by activities associated with the oil and natural gas industries and at hazardous waste sites. 2-Hexanone was detected in process water from a coal gasification site (7 µg/L) located in Wyoming and condensate water (202 µg/L) from the low-BTU gasification of coal from a facility in West Virginia (Pellizzari et al. 1979). It was also detected in retort water (55 µg/L) from an *in situ* oil shale processing location in Wyoming (Pellizzari et al. 1979). It was analyzed for, but not detected in, flowback water (the water that is returned to the surface following the hydraulic fracturing) from 19 natural gas hydraulic fracturing locations in West Virginia and Pennsylvania as well as flowback water from 5 locations in Texas (Hayes 2009; RPSEA 2012). The compound has also been tentatively identified in 1 of 63 industrial effluents (Perry et al. 1979), the effluent from a chemical plant (Shackelford and Keith 1976), and in one municipal landfill leachate at 0.148 ppm (mg/L) in a study of leachates from 58 municipal and industrial landfills (Brown and Donnelly 1988).

2-Hexanone has also been detected in both groundwater and surface water at hazardous waste sites (CLPSD 1989) (see Section 6.4.2), indicating that this is a source of 2-hexanone release to the environment.

6.2.3 Soil

There is no information on releases of 2-hexanone to the soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Soils or sediments may become contaminated with 2-hexanone by landfilling with 2-hexanone-containing solid wastes or by the discharge of contaminated water. 2-Hexanone has been detected in soil samples from hazardous waste sites (CLPSD 1989) (see Section 6.4.3).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

2-Hexanone exists in the atmosphere as a vapor. Liquid 2-hexanone is volatile; its vapor pressure has been measured as $1.53x10^{-2}$ atm (11.6 mmHg) at 25°C (Ambrose et al. 1975). Because 2-hexanone is very soluble in water, a large fraction of 2-hexanone released to the atmosphere, may dissolve in water vapor (such as clouds and rain drops). A Henry's law constant estimates the tendency of a chemical to partition between its vapor phase and water. An estimated value for Henry's law constant is $9.32x10^{-5}$ atm-m^3/mol at 25°C (HSDB 2009). The magnitude of this value suggests that a large fraction of vapor-phase 2-hexanone will dissolve in water, and that precipitation may be an important physical removal mechanism. An analogous air-water partition coefficient measured for 2-hexanone at 37°C was approximately $2.3x10^{-4}$ atm-m^3/mole (Sato and Nakajima 1979), which indicates that precipitation will also be an important removal mechanism at this higher temperature.

2-Hexanone is very soluble in water, approximately 17.2 g/L (Yalkowsky and Yan 2003). Henry's law constant indicates that a fraction of 2-hexanone will volatilize from water. Estimated half-lives in model river and lake water are about 7 hours and 7 days, respectively (Thomas 1990). Based on its estimated organic carbon partition coefficient (K_{oc}) value of 77, 2-hexanone is expected to have high mobility in soil (Thomas 1990), and may therefore leach into groundwater. This may be a particular concern if contaminated waste water or flowback water is stored in unlined containment ponds or disposed of via underground injection.

2-Hexanone is not likely bioconcentrated by organisms in water. An octanol/water partition coefficient (log K_{ow}) estimates the partitioning of a chemical between octanol and water. Octanol is believed to best imitate the fatty structures in plants and animal tissues. Generally, a log K_{ow} range of 2–7 describes most chemicals of interest with the potential to partition to fatty tissues. The log K_{ow} of 2-hexanone is 1.38 (Hansch et al. 1995). Therefore, this low value suggests that 2-hexanone is not likely to partition to fatty tissues. Further, a bioconcentration factor (BCF) relates the concentration of a chemical in plants or animals to the concentration of that chemical in the medium in which they live. Generally, a BCF value <30 is considered to have low bioconcentration potential. A BCF of 4 was calculated for 2-hexanone (EPA 2012c), suggesting that bioconcentration in aquatic organisms is not expected to be an important fate mechanism for 2-hexanone released into the environment. Biomagnification of 2-hexanone is also not expected to occur to any great extent (Lande et al. 1976). However, no experimental data on the biomagnification potential of 2-hexanone were located to corroborate these assumptions.

6.3.2 Transformation and Degradation

6.3.2.1 Air

The major fate mechanism of atmospheric 2-hexanone is photooxidation. This ketone is also degraded by direct photolysis (Calvert and Pitts 1966), but the reaction is estimated to be slow relative to reaction with hydroxyl radicals (Laity et al. 1973). The rate constant for the photochemically induced transformation of 2-hexanone by hydroxyl radicals in the atmosphere has been measured at 9.01×10^{-12} cm^3/ molecule-set (Atkinson 1989). Using an average concentration of atmospheric hydroxyl radicals of 5×10^5 molecules/cm^3 (Atkinson 1989), the calculated atmospheric half-life of 2-hexanone is about 2.4 days. However, the half-life may be shorter in polluted atmospheres with higher OH radical concentrations (MacLeod et al. 1984). Consequently, it appears that vapor-phase 2-hexanone is labile in the atmosphere.

6.3.2.2 Water

2-Hexanone is a ketone, and ketones are generally not degraded by hydrolysis (Lande et al. 1976). Based on its reactions in air, it seems likely that 2-hexanone will undergo photolysis in surface water, however no information was located. Based on studies with microorganisms (see Section 6.3.2.3), it is probable that 2-hexanone will be biodegraded in both surface water and groundwater.

6.3.2.3 Sediment and Soil

2-Hexanone may be biodegraded in soil. 2-Hexanone has been shown to be degraded by hydrocarbon-utilizing mycobacteria (Lukins and Foster 1963; Perry 1968). Similarly, certain yeasts have been isolated that can use 2-hexanone as a carbon source (Lowery et al. 1968). In a study using acclimated microbial cultures, 2-hexanone was significantly biodegraded (Babeu and Vaishnav 1987). An experimental 5-day biological oxygen demand (BOD) determination was about 61% of the theoretical BOD value. Although these studies have demonstrated that 2-hexanone may be biodegraded under ideal conditions, no information was located on its biological half-life in soils.

6.3.2.4 Other Media

No studies were located for the environmental fate of 2-hexanone in other media.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to 2-hexanone depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of 2-hexanone in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. Moreover, whether a substance such as 2-hexanone is detected in environmental media at a site or facility is a function of whether or not it is actually being monitored for. In reviewing data on 2-hexanone levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring 2-hexanone in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Limited studies were located that measured or estimated the concentration of 2-hexanone in ambient air. 2-Hexanone was detected, but not quantified, in air samples collected from Whitaker's Forest in the Sierra Nevada Mountains, California in 1990 (Helmig and Arey 1992).

2-Hexanone and several other volatile organic compounds (VOCs) were monitored for in Garfield County, Colorado where several natural gas hydraulic fracturing wells had been operating at the time of the study (ATSDR 2008). Natural gas needs to be separated from fluids and other gases that may release VOCs into the surrounding air. In addition, fracking water may contain small amounts of chemicals containing VOCs used during the hydraulic fracturing process, and these may volatilize to ambient air if the water is stored in uncovered wells at the location. 2-Hexanone was detected in 14.8% of grab samples collected at all of the monitoring sites in Garfield County at levels ranging from 0.7 to 15.0 $\mu g/m^3$, with an average concentration of 1.7 $\mu g/m^3$ (ATSDR 2008). It was concluded that noncancer adverse health effects were not likely to occur from exposure to the levels of 2-hexanone measured at these sites, based on comparison with the ATSDR chronic health guidelines. In addition to grab samples, 14 fixed sites were monitored for a 24-hour period once per month or once per quarter; this included 8 locations near oil and gas drilling facilities, 4 urban locations, and 2 rural background locations. 2-Hexanone was detected

in at least 4% of the samples from three of the oil and natural gas drilling locations and two of the urban locations. It was detected in <4% of the samples in both the rural background sites.

2-Hexanone was detected in ambient air during a monitoring study in the Commonwealth of Pennsylvania to determine the effect that natural gas exploration had on air quality (PA DEP 2011). Levels of 2-hexanone in air related to Marcellus Shale natural gas activities were determined to be at levels similar to, or slightly greater than, levels observed in areas not impacted by hydraulic fracturing operations. Annual average concentrations of 2-hexanone at these locations ranged from 0.11 to 2.1 µg/m^3. 2-Hexanone was detected in air samples above oil and gas waste water open containment ponds located in Kern County, California at a concentration of 12 µg/m^3 (Grinberg 2014).

In the past, workplace air concentrations in facilities where 2-hexanone was manufactured or used as a solvent ranged from 1 to 156 ppm (4.1–640 mg/m^3) (ACGIH 1986), and air concentrations up to 1,636 mg/m^3 were measured in the operations areas of some facilities (Bierbaum and Marceleno 1973; Marceleno et al. 1974). However, because 2-hexanone is no longer produced or used commercially in the United States, and because the federal government has set certain regulations and guidelines to help protect people from the possible health effects of 2-hexanone in the workplace, it is unlikely that current workplace air concentrations are as high as they were in the past. OSHA has set a Permissible Exposure Limit (PEL) of 100 ppm (100 parts of 2-hexanone in 1 million parts of air) as a time-weighted average (TWA) to this chemical in workplace air during an 8-hour work period, over a 40-hour workweek (OSHA 2015b). NIOSH has set a Recommended Exposure Limit (REL) of 1 ppm (TWA) 2-hexanone in work place air as an average exposure during a 10-hour work period (NIOSH 2015) for up to a 40-hour workweek. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a 5 ppm (TWA) Threshold Limit Value (TLV) for 2-hexanone in workplace air as an average during an 8-hour work day (ACGIH 2001, 2003, 2015). ACGIH also has a 15-minute short-term exposure limit (STEL) of 10 ppm.

6.4.2 Water

2-Hexanone was 1 of 70 VOCs monitored for in influent water and flow-back water at 19 hydraulic fracturing locations located in Pennsylvania and West Virginia (Hayes 2009). 2-Hexanone was not detected in the samples collected. It was also not detected in flowback water from five hydraulic fracturing operations in North Texas (RPSEA 2012).

Data estimating 2-hexanone concentrations in water are sparse. 2-Hexanone was identified in one of three groundwater samples at a concentration of 87 µg/L (ppb) near a hazardous waste site in Florida (Myers 1983). 2-Hexanone was detected, but not quantified, in groundwater near a forest waste site in Otisville, Michigan in 1987 (EPA 1988). Groundwater samples collected from the Biscayne Aquifer Superfund sites in Florida contained 2-hexanone at maximum concentrations of 150 µg/L (from the entire study area) and 110 µg/L (from well fields) (Canter and Sabatini 1994). 2-Hexanone was detected in 0.3, 11.1, 3.6, and 1.4% of hazardous waste site groundwater samples collected from 1981 to 1986 in EPA Regions 1, 2, 9, and 10, respectively (Plumb 1992).

2-Hexanone was detected at an unauthorized hazardous waste disposal site in Lang Township, New Jersey in two well water samples collected in 1985 at an average concentration of 7,135 µg/L (maximum concentration of 14,000 µg/L) and in onsite lagoon surface water samples at an average concentration of 20 µg/L (maximum concentration of 30 µg/L) (U.S. EPA 1986). This compound was also identified in a study of drinking water concentrates and advanced waste treatment concentrates (Lucas 1984). Richardson et al. (1999) reported that 2-hexanone was identified in drinking water that had been treated by ozone disinfection.

6.4.3 Sediment and Soil

2-Hexanone was detected in soil samples at 3% of hazardous waste sites (both NPL and non-NPL) at a geometric mean concentration of 40 µg/kg (ppb) in positive samples (CLPSD 1989). 2-Hexanone was detected at an unauthorized hazardous waste disposal site in Lang Township, New Jersey in surface and subsurface soil samples collected in 1985 at concentrations of 440 and 46 µg/kg, respectively (EPA 1986). In residential topsoil samples taken from a 0.5-acre area at the Dona Park Residential site located immediately south of a former smelting and refining plant in Corpus Christi, Texas, 2-hexanone was detected at 274 mg/kg (TCEQ 2011). No other data were located regarding estimation of 2-hexanone in soils or sediments.

6.4.4 Other Environmental Media

2-Alkanones and 2-alkanols are formed naturally in some foods as a byproduct of the degradation of free fatty acids (Dumont and Adda 1978; Girolami and Knight 1955). 2-Hexanone has been identified among the natural volatile components of several foods, including blue and Beaufort cheeses, nectarines, roasted filberts (hazelnuts), beef, and chicken muscle (Day and Anderson 1965; Dumont and Adda 1978; Grey and Shrimpton 1967; Kinlin et al. 1972; Ramarathnam et al. 1991; Takeoka et al. 1988); levels were not

stated in these reports. It has been detected in canned cream, canned kernel, frozen kernel, and fresh kernel cooked corn products at concentrations of 1, 2, <5, and <1 ppb, respectively (Buttery et al. 1994). 2-Hexanone was also detected in milk and cream at concentrations ranging from 0.007 to 0.018 ppm (7–18 ppb) and in bread (Lande et al. 1976). Because few quantitative data are available, it is not known if food is an important source of human exposure to 2-hexanone.

No studies were located regarding the occurrence of 2-hexanone in any other media.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Human exposure to 2-hexanone may occur by inhalation, ingestion, or dermal exposure. Exposure to small amounts of 2-hexanone may occur by ingestion of foods in which it has been detected. However, since this compound is no longer manufactured or used commercially in the United States after its discontinuation in 1979 (EPA 1987), widespread or high-level exposure of the general population to 2-hexanone is not likely. 2-Hexanone has been detected in air samples at locations in which hydraulic fracturing has occurred, suggesting that nearby populations could be susceptible to inhalation exposure. No data were located indicating that 2-hexanone has been detected in groundwater at these locations.

According to surveys conducted by NIOSH, the number of employees potentially exposed to 2-hexanone dropped from 41,600 in the early 1970s to 1,100 in the early 1980s (RTECS 2009). Neither the National Occupational Hazard Survey (NOHS) nor the National Occupational Exposure Survey (NOES) databases contain information on the frequency, concentration, or duration of exposures of workers to any chemicals listed. These surveys provide only estimates of the number of workers potentially exposed to chemicals in the workplace. This dramatic reduction in the extent of occupational exposure parallels the halt of production and the reduction in commercial use of this chemical (EPA 1987). It is unlikely that many persons are currently occupationally exposed to 2-hexanone, other than as a degradation product resulting from wood pulping, *in situ* oil shale processing, or coal gasification operations. NIOSH does not list 2-hexanone among the chemicals considered in an occupational exposure evaluation of coal gasification plants (NIOSH 1978).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume than adults. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and may spend more time outdoors. Children also are generally closer to the ground and have not yet developed the adult capacity to judge and take actions to avoid hazards (NRC 1993).

Children are expected to be exposed to 2-hexanone by the same routes that affect adults. Ingestion of foods contaminated with small amounts of 2-hexanone is the most likely route of exposure for children. No data were located regarding 2-hexanone in breast milk; therefore, an adequate determination of the importance of this route of child exposure has not been made.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Populations with potentially high exposure to 2-hexanone include people living near or working in areas affected by oil and natural gas activities, or living near the hazardous waste sites where 2-hexanone is likely present. The most likely exposure routes are ingestion or dermal contact with water contaminated from these sources or inhalation of 2-hexanone that has volatilized from contaminated water or soil. Individuals may still be exposed by ingestion, inhalation, skin absorption from use of consumer products manufactured prior to 1982 such as lacquers, primers, sealers, and thinners that contain 2-hexanone, or through currently imported products containing 2-hexanone, including foods.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 2-hexanone is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 2-hexanone.

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.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical property data available for 2-hexanone are sufficient to allow a limited estimation of the potential environmental fate of this chemical. The estimated Henry's law constant (EPA 2012c) and K_{oc} (Thomas 1990) need to be verified experimentally to help confirm the estimates of partitioning in environmental media.

Production, Import/Export, Use, Release, and Disposal. No information is available in the TRI database on facilities that manufacture or process 2-hexanone because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005).

2-Hexanone is no longer produced, imported, or used commercially in the United States (EPA 1987). Any future manufacture or use is required to be reported to EPA (EPA 1987). Data from these reports would be helpful in estimating the potential for human exposure to this compound. No data on disposal of 2-hexanone were located. Information on disposal practices for wastes containing 2-hexanone is necessary for estimations of human exposure from this source. No regulations govern the disposal of 2-hexanone.

Environmental Fate. The probable transport and partitioning of 2-hexanone in environmental media have been predicted based on estimated partition coefficients. Experimental confirmation of these values would help to increase the accuracy of transport and partitioning assessments. The loss mechanisms of 2-hexanone transformations in the atmosphere are fairly-well understood (Atkinson et al. 1985; Calvert and Pitts 1966; Laity et al. 1973; MacLeod et al. 1984), but the reaction pathways and environmental fates of the transformation products are not known. Very little is known about the fate of 2-hexanone in water or soil (Babeu and Vaishnav 1987; Lande et al. 1976; Lowery et al. 1968; Lukins and Foster 1963; Perry 1968). Data on photodegradation and biodegradation of 2-hexanone in surface water and biodegradation

of 2-hexanone in groundwater and soil may be helpful in assessing the persistence of 2-hexanone in these media.

Bioavailability from Environmental Media. Information on absorption by humans and other animal species indicates that it is well absorbed via the oral and dermal routes (DiVincenzo et al. 1977, 1978). 2-Hexanone has also been demonstrated to be well absorbed by humans and animals following inhalation exposure (DiVincenzo et al. 1978). Information on its bioavailability from contaminated soils would be useful in assessing the risk from exposure to this medium by populations in the vicinity of hazardous waste sites likely contaminated with 2-hexanone.

Food Chain Bioaccumulation. There are no data on the bioaccumulation of 2-hexanone in food chains. This lack of data may not be a major limitation in the database because it is unlikely that 2-hexanone is bioconcentrated by plants, aquatic organisms, or animals at lower trophic levels based on its high water solubility (Lande et al. 1976). However, data confirming that bioconcentration does not occur would help to more accurately assess the probability of bioaccumulation of 2-hexanone.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of 2-hexanone in contaminated media at hazardous waste sites are needed so that the information obtained on levels of 2-hexanone in the environment can be used in combination with the known body burden of 2-hexanone to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Very few data are available regarding the presence of 2-hexanone in any environmental media (CLPSD 1989; Lucas 1984; Myers 1983). Although high levels of this compound are not expected to occur in ambient air, water, or soil, concentrations of 2-hexanone in these media near effluent sources or hazardous waste sites would be helpful in assessing the potential extent and magnitude of human exposures.

Exposure Levels in Humans. No information has been located on exposure levels of humans to 2-hexanone in the workplace or in the vicinity of hazardous waste sites. It would be useful to collect information on levels of exposure to 2-hexanone in the environment and associated blood, urine, or tissue levels of 2-hexanone and/or its metabolites in the exposed populations. Additional information relating those levels to the subsequent development of health effects would also be extremely useful.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. No information has been located on exposure levels of children to 2-hexanone in the vicinity of hazardous waste sites. It would be useful to collect information on levels of exposure to 2-hexanone in the environment and associated blood, urine, or tissue levels of 2-hexanone and/or its metabolites in the exposed populations. Additional information relating those levels to the subsequent development of health effects would also be extremely useful.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. The information 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; however, no exposure registries for 2-hexanone were located. 2-Hexanone is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. 2-Hexanone will be considered in the future when chemical selection is made for sub-registries to be established.

6.8.2 Ongoing Studies

No ongoing studies regarding its environmental fate or physical properties were identified in the NIH RePORTER (2016) database.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring 2-hexanone, its metabolites, and other biomarkers of exposure and effect to 2-hexanone. 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.

7.1 BIOLOGICAL MATERIALS

In biological systems in which 2-hexanone may have been metabolized to 2,5-hexanedione consideration must be given to possible binding of the analyte as a glucuronide conjugate. In such cases, 2-hexanone may be released by hydrolysis with acid (Fedtke and Bolt 1986). Following pre-treatment, which varies with the sample and may include homogenization, centrifugation, and acidification, 2-hexanone can be released from biological samples by purging or perfusion and trapped on a sorbent, extracted with a solvent such as acetone, or extracted directly onto sorbent solids.

Sensitive and selective methods are available for the qualitative and quantitative measurement of 2-hexanone via its metabolite, 2,5-hexanedione, after it is separated from its sample matrix. Gas chromatography (GC) using sensitive and highly specific mass spectrometry (MS) or highly sensitive flame ionization detection (FID) is the analytical method most commonly used. Capillary gas chromatography, also known broadly as high resolution gas chromatography (HRGC), has greatly facilitated the analysis of compounds such as 2-hexanone that can be measured by gas chromatography and has resulted in vast improvements in resolution and sensitivity. It has made the choice of a stationary phase much less crucial than is the case with the older method using packed columns. The instrumental capability to separate volatile analytes by HRGC is, for the most part, no longer the limiting factor in their analysis. High performance liquid chromatography (HPLC) may also be used and has the advantage of compatibility with the liquid matrix of biological samples.

Methods for detection of 2-hexanone via its metabolite, 2,5-hexanedione, in biological materials are summarized in Table 7-1.

7.2 ENVIRONMENTAL SAMPLES

For the determination of 2-hexanone in air, the analyte is usually trapped and concentrated from a large volume of air on a solid sorbent such as Tenax® or activated carbon from which it can be released thermally or eluted with a solvent such as carbon disulfide for subsequent measurement (NIOSH 1984, 2003; OSHA 1995). For aqueous samples, 2-hexanone is purged with an inert gas and collected on a solid such as Tenax®, followed by thermal desorption and measurement. Cryogenic trapping has also been used for removal of 2-hexanone from water samples (Badings et al. 1985). GC using sensitive and highly specific MS or highly sensitive FID is the analytical method of choice for the determination of 2-hexanone in environmental samples.

Methods for the determination of 2-hexanone in environmental samples are summarized in Table 7-2.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 2-hexanone is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 2-hexanone.

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.

Table 7-1. Analytical Methods for Determining 2-Hexanone in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Hydrolysis of metabolic conjugates with HCl, extraction on Cl8 cartridge, desorption	HGRC/MS	0.05–0.08 µg/mL	81±3.2%[a]	Fedtke and Bolt 1986
Biological samples (chicken plasma)[b]	Extraction with ether after addition of HCl and Na_2SO_4, concentrated under N_2	HGRC/FID	No data	78±4%[c]	Nomeir and Abou-Donia 1985
Biological samples (chicken plasma)[b]	Extraction with ether after addition of HCl and Na_2SO_4, concentrated under N_2	HPLC/UV	No data	No data	Nomeir and Abou-Donia 1985
Biological samples (blood, brain, kidney, liver)[b]	Homogenization with acetone, centrifugation, injection of acetone extract	GC/MS	No data	98±12–110±16%[d]	White et al. 1979
Blood (human)[e]	Perfusion at 95°C, collection on Tenax®, release by heating	GC/MS	No data	No data	Anderson and Harland 1980

[a]Percent recovery for 2,5-hexanedione was 83±3.6%.
[b]This method was also used in the determination of 2,5-hexanedione, a metabolic product of 2-hexanone.
[c]Percent recovery for 2,5-hexanedione was 62±3%.
[d]Percent recovery for 2,5-hexanedione was 96±13–100±16%.
[e]$C_6H_{12}O$ ketone detected in blood of five cadavers at necropsy.

FID = flame ionization detector; GC = gas chromatography; HPLC = high-performance liquid chromatography; HRGC = high resolution gas chromatography; MS = mass spectrometry; UV = ultraviolet

Table 7-2. Analytical Methods for Determining 2-Hexanone in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Air is drawn through a charcoal tube; desorption 1:99 dimethyl formamide: carbon disulfide	GC/FID (Method PV2031)	0.454 µg (0.227 mg/m^3)	93.5%	OSHA 1995
Air	Air is drawn through a solid Anasorb CMS sorbent tube; elution with carbon disulfide	GC/FID (Method 2555)	0.9 µg	100.6% (RSD=0.011)	NIOSH 2003
Air	Retention by activated carbon, elution with carbon disulfide	GC/FID (Method 1300)	20 µg	No data	NIOSH 1984
Water, environ-mental samples	Purge, cryogenic trap	HRGC	<10 µg/kg	No data	Badings et al. 1985
Groundwater	Purge by helium, collection on solid, thermal desorption	GC/MS (Method 1624)	50 µg/L	No data	EPA 1986
Waste water and spent oil shale	Collection on Tenax®, thermal desorption	HRGC/FID; GC/MS	No data	No data	Hawthorne et al. 1985
Solid waste	Purge by helium, collection on solid, thermal desorption	GC/MS (Method 1624)	50 µg/L	No data	EPA 1986

FID = flame ionization detector; GC = gas chromatography; HRGC = high-resolution gas chromatography; MS = mass spectrometry

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. As noted in Section 7.1, methods are available for the qualitative and quantitative measurement of 2-hexanone after it is separated from its sample matrix (Anderson and Harland 1980; Fedtke and Bolt 1986; Nomeir and Abou-Donia 1985; White et al. 1979). HRGC for 2-hexanone analysis has been developed to the point that the instrumental capability to separate volatile analytes by HRGC is, for the most part, no longer the limiting factor in their analysis. FID has enabled detection at very low levels, and MS has assured specificity in measurement.

More specific methods to determine biomarkers of exposure to 2-hexanone would be helpful in detecting exposure to this compound before adverse morphological or clinical effects occur. Finding biological markers of exposure to 2-hexanone is complicated by the fact that this compound is itself a biological indicator of exposure to *n*-hexane (Fedtke and Bolt 1986). In addition, the presence of the metabolite, 2,5-hexanedione, may indicate exposure to 2-hexanone, but it is also a biological indicator of exposure to *n*-hexane (Fedtke and Bolt 1986). There is insufficient information in the literature to determine if methods for determining biomarkers of exposure and effect of 2-hexanone are sensitive enough to measure background levels in the population and levels at which biological effects occur. The precision, accuracy, reliability, and specificity of these methods are not sufficiently documented. This information would be valuable for interpreting monitoring data.

Refinement of existing purge-and-trap extraction techniques and investigation of alternative concentration methods such as cryotrapping (Pankow and Rosen 1988) and supercritical fluid extraction (King 1989) would be useful. In addition, several major challenges remain. One of these is to transfer analytes that have been isolated from a biological or environmental matrix quantitatively and in a narrow band to the HRGC. Another major challenge is to identify and accurately measure the quantity of compounds in the HRGC peaks. MS detection has been outstanding for identification, but other techniques, particularly Fourier transform infrared spectroscopy (FTIR), may offer some advantages (Wieboldt et al. 1988).

Metabolites of 2-hexanone in biological materials are difficult to determine in routine practice because of the lack of standardized methods for their measurement. As shown in Table 7-1, there are very few well characterized methods for the determination of metabolites of 2-hexanone in biological materials (Nomeir

and Abou-Donia 1985; White et al. 1979). The precision, accuracy, reliability, and specificity of existing methods need to be evaluated, and the methods refined and adapted to routine practice.

Effect. There are currently no subtle or sensitive biomarkers of effects associated with exposure to 2-hexanone. Electromyographic testing, however, may prove to be useful in the detection of nerve conduction abnormalities in their early stages, even before they are accompanied by clinical manifestations. Specific electrodiagnostic patterns associated with exposure to 2-hexanone have not been clearly delineated.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. The media of most concern for human exposure to 2-hexanone are drinking water (primarily from groundwater sources) and air. From the data presented in Table 7-2 (Badings et al. 1985; EPA 1986; Hawthorne et al. 1985; NIOSH 1984), it may be concluded that the methods available for the determination of 2-hexanone in water and air are not sensitive enough to determine background levels of this compound. Existing methods are satisfactory for measuring levels at which health effects occur.

The precision, accuracy, reliability, and specificity of methods to determine 2-hexanone in water and air are not well documented, and additional work is needed in this area.

Methods for determining the parent compound, 2-hexanone, in water, air, and waste samples are available (Badings et al. 1985; EPA 1986; Hawthorne et al. 1985; NIOSH 1984). Sampling methodologies for compounds such as 2-hexanone continue to pose problems such as nonrepresentative samples, insufficient sample volumes, contamination, and labor-intensive, tedious extraction and purification procedures (Green and Le Pape 1987). It would be helpful to have means to measure organic compounds such as 2-hexanone *in situ* in water and other environmental media without the need for sampling and extraction procedures to isolate the analyte prior to analysis.

7.3.2 Ongoing Studies

Ongoing research identified in the NIH RePORTER (2016) includes a project aimed at developing sperm molecular biomarkers to improve detection and monitoring of testicular toxicants associated with hazardous waste sites. The research aims to improve monitoring capability for workers and the general population in order to prevent toxicant-induced testicular damage from chronic low-level exposures to environmental chemicals.

8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance-specific estimates that are intended to serve as screening levels. They are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

The international and national regulations, advisories, and guidelines regarding 2-hexanone in air, water, and other media are summarized in Table 8-1.

ATSDR has derived a chronic-duration oral provisional MRL of 0.05 mg/kg/day for 2-hexanone based on a LOAEL of 143 mg 2-hexanone/kg/day for peripheral neuropathy in male Sprague-Dawley rats exposed via the drinking water for 13 months (O'Donoghue et al. 1978). A combined uncertainty factor of 1,000 was used (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) and a modifying factor of 3 (for achieving an 80% response rate with the lowest dose).

EPA (IRIS 2009) derived a reference dose (RfD) of 0.005 mg/kg/day for 2-hexanone (last revised 09/25/2009) based on a $BMDL_{10}$ of 5 mg/kg/day for peripheral neuropathy in Sprague Dawley rats treated with 2-hexanone in the drinking water for 13 months (O'Donoghue et al. 1978). An uncertainty factor of 1,000 was used (10 for animal to human extrapolation, 10 for human variability, and 10 for database deficiencies).

EPA (IRIS 2009) derived a reference concentration (RfC) of 0.03 mg/m^3 for 2-hexanone (last revised 09/25/2009) based on a $BMCL_{05[HEC]}$ of 90 mg/m^3 for reduced motor nerve conduction velocity in male monkeys (*Macaca fascicularis*) exposed to 2-hexanone vapors for 6 months (Johnson et al.1977). An uncertainty factor of 3,000 was used (3 for animal to human extrapolation, 10 for human variability, 10 for subchronic to chronic extrapolation, and 10 for database deficiencies).

Table 8-1. Regulations, Advisories, and Guidelines Applicable to 2-Hexanone

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2016
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines	No data	WHO 2011
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	5 ppm (20 mg/m^3)[a]	ACGIH 2001, 2003, 2015
	STEL (15-minute TWA)	10 ppm (40 mg/m^3)[a,b]	
	BEI	0.4 mg/L[c]	
AIHA	ERPGs	No data	AIHA 2015
TERA	WEELs	No data	TERA 2014
DOE	PACs		DOE 2016
	PAC-1[d]	10 ppm	
	PAC-2[d]	830 ppm	
	PAC-3[d]	5000 ppm	
EPA	AEGLs	No data	AEGLs 2016
	Hazardous air pollutant	No data	EPA 2014 42 USC 7412
NIOSH	REL (up to 10-hour TWA)	1 ppm (4 mg/m^3)	NIOSH 2015
	IDLH	1600 ppm	NIOSH 2014
OSHA	PEL (8-hour TWA) for general industry	100 ppm (410 mg/m^3)	OSHA 2015b 29 CFR 1910.1000, Table Z-1
	PEL (8-hour TWA) for shipyards	100 ppm (410 mg/m^3)	OSHA 2015c 29 CFR 1915.1000 Table Z
	PEL (8-hour TWA) for construction	100 ppm (410 mg/m^3)	OSHA 2015a 29 CFR 1926.55 Appendix A
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	No data	EPA 2015a 40 CFR 116.4
	Drinking water standards and health advisories	No data	EPA 2012b
	National primary drinking water standards	No data	EPA 2009b
	National recommended water quality criteria	No data	EPA 2016a, 2016b

Table 8-1. Regulations, Advisories, and Guidelines Applicable to 2-Hexanone

Agency	Description	Information	Reference
NATIONAL (*cont.)*			
EPA (*cont.*)	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	No data	EPA 2015b 40 CFR 117.3
c. Food			
FDA	EAFUS	No data[e]	FDA 2013
d. Other			
ACGIH	Carcinogenicity classification	No data	ACGIH 2015
EPA	Carcinogenicity classification	Database is inadequate to assess human carcinogenic potential	IRIS 2009
	RfC	$3x10^{-2}$ mg/m^3	
	RfD	$5x10^{-3}$ mg/kg/day	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity	No data	EPA 2015c 40 CFR 302.4
	Effective date of toxic chemical release reporting	No data	EPA 2015d 40 CFR 372.65
	TSCA chemical lists and reporting periods	No data	EPA 2015e 40 CFR 712.30
DHHS	Carcinogenicity classification	No data	NTP 2014

[a]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors or, of probable greater significance, by direct skin contact with the substance.
[b]Should not be exceeded at any time during a workday.
[c]2,5-Hexanedione without hydrolysis in urine collected at end of shift at end of workweek.
[d]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2012).
[e]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; BEI = biological exposure index; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DHHS = Department of Health and Human Services; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health concentrations; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TERA = Toxicology Excellence for Risk Assessment; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; WEEL = Workplace Environment Exposure Level; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

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

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

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 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.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

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.

Biomarkers—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.

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.

Case-Control Study— A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

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

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

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.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

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 occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (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.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

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

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

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

***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 that 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 has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that 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 exposure level 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.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

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

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a 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.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

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

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

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 no-observed-adverse-effect level (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 the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 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 hazardous substance. 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.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

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)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxic Dose$_{(50)}$ (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.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) 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 lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (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 for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

Although acute-, intermediate-, and chronic-duration studies are available for inhalation and oral exposure to 2-hexanone, the databases were only considered adequate for derivation of a chronic-duration inhalation MRL. This MRL is discussed in the MRL worksheet in this Appendix. The rationales for not deriving MRLs for the other inhalation exposure durations and for oral exposure are included in Section 2.3 of the profile.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 2-Hexanone
CAS Numbers: 591-78-6
Date: April 2018
Profile Status: Final, Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 14
Species: Rat

Provisional Minimal Risk Level: 0.05 [X] mg/kg/day [ ] ppm

Reference: O'Donoghue JL, Krasavage WJ, Terhaar C.J. 1978. A comparative chronic toxicity of methyl n-propyl ketone, methyl n-butyl ketone and hexane by ingestion. Eastman Kodak Company, Rochester, NY; Report No. 104657Y. Submitted under TSCA Section 8ECP; EPA Document No. 88-920008233; NTIS No. OTS0555051. Unpublished study.

Experimental design: Groups of male Sprague-Dawley rats (10/group) drank water containing 0, 0.25, 0.5, or 1.0% 2-hexanone (96.1% purity) for 13 months. Based on water consumption and body weight data, the investigators calculated the water provided doses of 0, 143, 266, or 560 mg 2-hexanone/kg/day. There were two control groups, each with 10 rats. Rats were observed daily for clinical signs; body weight measurements and neurological examinations were performed weekly. At termination of exposure, the hindlimb sciatic-plantar nerve, multiple levels of the spinal cord, medulla, and cerebellum from five rats per group were embedded in plastic for microscopic examination. Most tissues and organs from the highest dose group and target organs from lower dose groups were embedded in paraffin for light microscopy examination.

Effect noted in study and corresponding doses: Clinical signs were restricted to neurological effects and reduced body weight. Final body weights were reduced approximately 6, 14, and 30% in the low-, mid-, and high-dose groups, respectively. No information was provided regarding food consumption. Clinical neurological signs were seen in the mid- and high-dose groups. Signs first appear on day 42 in the high-dose groups and on day 77 in the mid-dose group. All rats in the high-dose group showed severe deficits. Signs included decreased extension of hindlimbs, hindlimb weakness, waddling gait, dragging of hind paws, loss of tone in hindlimb musculature with grossly observable atrophy of hindlimb musculature and axial muscles of the lumbar area. Weakness of the forelimbs was seen in three out of nine high-dose rats by the end of the study. No clinical progression was apparent in the mid-dose group. Histological examination showed that rats from all treated groups had "giant' axonal neuropathy. Axonal swelling and giant axonopathy were common in peripheral nerves and spinal cord from high-dose rats, less common in dorsal root ganglia, and rare in the brain. Sections embedded in plastic showed clumping of axonal organelles. Myelin alterations were also seen in peripheral nerves. Neurogenic skeletal muscle atrophy occurred in proximal and distal hindlimb musculature. Alterations in the mid-dose group were similar but less severe. Less severe changes were seen in peripheral nerves from low-dose rats; fewer giant axons were evident, but myelin changes were more common. Spinal lesions and neurogenic muscle atrophy were minimal. Relevant incidence data are shown in Table A-1. No treatment-related gross or microscopic alterations were reported in tissues other than the nervous system and skeletal muscle.

Table A-1. Incidence Data for Neuropathological Lesions in Rats exposed to 2-Hexanone for 13 Months

	Axonal swelling				Myofibrillar atrophy	
Dose (mg/kg/day)	Brain	Spinal cord	Dorsal root ganglia	Peripheral nerve	Quadriceps muscle	Calf muscle
0	0/10	0/5	0/5	0/10	0/10	0/10
143	2/10	7/10[a]	0/7	8/10[a]	1/10	2/10
266	4/10[a]	5/5[a]	0/5	10/10[a]	5/10[a]	6/10[a]
560	8/10[a]	5/5[a]	3/5	10/10[a]	10/10[a]	10/10[a]

[a]p<0.05 per Fisher Exact Test conducted by SRC, Inc.

Source: O'Donoghue et al. 1978

BMD modelling of the incidence data for axonal swelling in peripheral nerve of rats in the O'Donoghue et al. (1978) study was considered and rejected because a nearly maximum response level (80%) was reached with the lowest dose tested. In such cases, there is great uncertainty because the BMD may be just below the first dose or orders of magnitude lower (EPA 2012a). Therefore, the NOAEL/LOAEL approach was used to derive a chronic-duration oral provisional MRL for 2-hexanone. Applying a combined uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 for human variability) and a modifying factor of 3 (to account for an 80% response rate at the lowest dose) to the LOAEL of 143 mg/kg/day results in a chronic-duration oral provisional MRL of 0.05 mg/kg/day for 2-hexanone.

Dose and end point used for MRL derivation: LOAEL of 143 mg/kg/day for peripheral neuropathy in male rats.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability
[X] 3 to account for an 80% response rate with the lowest dose

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Conversion was done by the investigators.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: 2-Hexanone is a well-known neurotoxicant that has been tested in a variety of animal species exposed orally (Abdel-Rahman et al. 1978; Eben et al. 1979; Krasavage et al. 1980; Union Carbide 1977) and by inhalation (Allen et al. 1975; Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Krasavage and O'Donoghue 1977; Mendell et al. 1974b; O'Donoghue and Krasavage 1979; Saida et al. 1976). Because

the toxic chemical form of 2-hexanone is the metabolite, 2,5-hexanedione, and 2,5-hexanedione is also a metabolite of *n*-hexane, additional relevant information can be found in documents on *n*-hexane (i.e., ATSDR 1999).

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical 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 chemical.

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

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, 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 chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

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. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and 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.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "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 that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive 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 systemic, neurological, and developmental effects. If this 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 no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the 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 levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, 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. Use the LSE tables and figures 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. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(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. Typically 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 Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures include 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 (see key number 18).

(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 derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens 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 “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse 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 LOAEL is the lowest dose used in the study that caused an adverse 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 respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

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

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured 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, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. 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 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. 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 the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

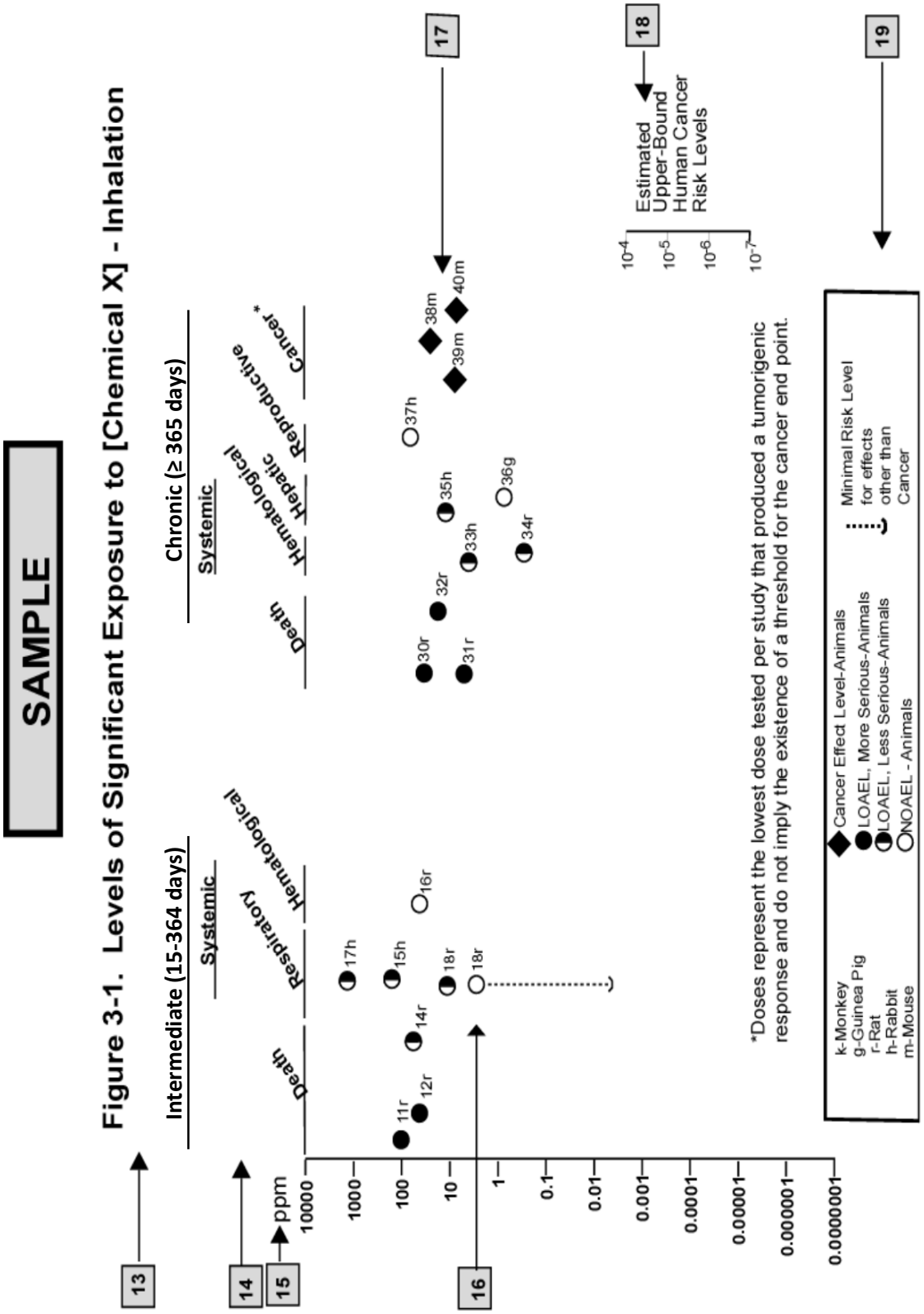
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ 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).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans*,*trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell

WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result