DRAFT
TOXICOLOGICAL PROFILE FOR
ACROLEIN

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

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UPDATE STATEMENT

A Toxicological Profile for Acrolein was released in 1990. This 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 Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE
Mailstop F-32
Atlanta, Georgia 30333

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 the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous 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 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 hazardous 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.

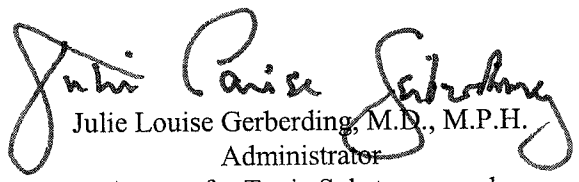
The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available.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

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mail Stop F-32
Atlanta, Georgia 30333

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 7, 2003 (68 FR 63098). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792); and October 25, 2001 (66 FR 54014). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff 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.



Julie Louise Gerberding, M.D., M.P.H.
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Agency for Toxic Substances and
Disease Registry

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 will 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 (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:

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**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:	1-888-42-ATSDR or (404) 498-0110	***Fax:***	(770) 488-4178
E-mail:	atsdric@cdc.gov	***Internet***:	http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental*

Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.

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. 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.

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.

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, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-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.

Referrals

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.

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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 Research Implementation 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.

PEER REVIEW

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

1. Ghulam Ahmad Shakeel Ansari, Ph.D., Department of Human Biological Chemistry and Genetics, Department of Pathology, University of Texas Medical Branch, Galveston, Texas;

2. James Kehrer, Ph.D., Professor of Pharmacology, Center for Molecular and Cellular Toxicology, The University of Texas at Austin, Austin, Texas; and

3. John Morris, Ph.D., Department of Pharmaceutical Sciences, University of Connecticut, School of Pharmacy, Storrs, Connecticut.

These experts collectively have knowledge of acrolein'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

This public health statement tells you about acrolein and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Acrolein has been found in at least 31 of the 1,662 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which acrolein is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to acrolein, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS ACROLEIN?

Acrolein is a clear or yellow liquid with a burnt, sweet, pungent odor. Most people begin to smell acrolein in air at concentrations of 0.25 parts acrolein per million parts of air (ppm). It ignites and burns easily in air. Acrolein changes into a vapor much faster than water does at normal temperatures. The change of acrolein from a liquid to a vapor becomes faster as temperature increases. Acrolein might be found in the air, water, or soil near hazardous waste sites if it was not properly stored. Although acrolein may be found in surface water and soil, it

can quickly evaporate or can be rapidly inactivated by binding to materials in soil; as such, it is not likely to last a long time in the environment.

Acrolein is primarily used to make other chemicals and may also be found in some livestock feed. Acrolein is itself a pesticide and is added to irrigation canals and the water supplies of some industrial plants to control underwater plant, algae, and slime growth. At much higher concentrations, it is used to make chemical weapons.

Small amounts of acrolein can be formed and can enter the air when organic matter such as trees and other plants (including tobacco) are burned and also when fuels such as gasoline and oil are burned. Acrolein is also formed in building fires at concentrations that can be deadly for occupants. Please refer to Chapters 4, 5, and 6 for more information.

1.2 WHAT HAPPENS TO ACROLEIN WHEN IT ENTERS THE ENVIRONMENT?

Acrolein can enter the environment as a result of burning wood, tobacco, vehicle fuels; overheating or burning of cooking oils; and accidental release from chemical plants or release from a hazardous waste site. Acrolein that enters the air as a vapor changes into other chemicals within days. When acrolein is introduced into water, it dissolves easily. Some of the acrolein in water changes into a vapor and enters the air. The acrolein left in the water is changed into other chemicals, which are rapidly broken down, or it may be removed by binding to substances in water.

Acrolein that enters the soil can change into vapor and enter the air, be washed out with water, or may bind to soils in such a way as to make it non-toxic. Please refer to Chapter 6 for more information.

1.3 HOW MIGHT I BE EXPOSED TO ACROLEIN?

If you live near a hazardous waste site in which acrolein is not stored properly, you could be exposed to acrolein from breathing air or drinking water that contains acrolein. Because acrolein easily changes into a vapor, you are more likely to be exposed to it from breathing air than from drinking water. A child playing in this hazardous waste site could be exposed to acrolein by drinking surface water, eating soil, or having skin contact with soil that contains acrolein. However, unless a large amount of acrolein was released at the site, it is unlikely that children would be exposed to acrolein in soil given that the acrolein vaporizes from the surface of the soil or is changed by binding with soil.

Acrolein is formed by the breakdown of many pollutants found in outdoor air. Burning tobacco and other plants forms acrolein. You breathe in acrolein when you smoke tobacco or when you are near someone who is smoking (secondhand smoke). You also breathe in acrolein when you are near automobiles, because burning gasoline forms acrolein which enters the air. However, the amount of acrolein in automobile exhaust tends to be very low. Your own body can produce very small amounts of acrolein when certain fatty molecules or amino acids are broken down. If you live near an oil or coal power plant, you breathe in small amounts of acrolein. You could breathe in acrolein if you work in an industry that uses acrolein to make other chemicals.

Acrolein is formed when fats are overheated. Small amounts of acrolein may also be found in foods such as fried foods, cooking oils, and roasted coffee. Although we know acrolein is in certain foods, the amount that is in the foods that you eat is not known.

The levels of acrolein are usually low in outside air, averaging around 0.20 parts acrolein in one billion parts air (0.2 ppb) in urban air and 0.12 ppb in rural air. However, in several large cities acrolein has been measured at levels of 5.6 ppb. The levels of acrolein within the air of a typical home range between less than 0.02 and 12 ppb but can be higher if you smoke tobacco in your home.

Acrolein has not been found in drinking water, and it is not commonly found in surface waters such as lakes and streams. The background levels of acrolein in these waters or in soil are not known.

Please refer to Chapter 6 for more information on how you might be exposed to acrolein.

1.4 HOW CAN ACROLEIN ENTER AND LEAVE MY BODY?

If you breathed in acrolein, most of it would enter your body's tissues within seconds. If you swallowed acrolein or spilled it on your skin, some of it would rapidly enter your body's tissues, but we do not know how much. Once in your body tissues, acrolein changes into other chemicals called metabolites. This probably occurs within minutes or hours. Some of these metabolites leave your body in your urine. It is not known how long this takes. For further information on how acrolein can enter and leave your body, see Chapter 3.

1.5 HOW CAN ACROLEIN AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

How a chemical affects your health depends on the amount and length of time of exposure. As you are exposed to more acrolein, and for a longer period of time, the effects that you experience

are likely to become worse. If you breathed in low levels of acrolein for a short time, your eyes might water and your nose and throat might become sore. These effects disappear within minutes after the exposure stops. However, if you were exposed to higher levels, your lungs might be affected more severely and for a longer time. Breathing in very high levels of acrolein might affect your lungs so severely that you might die.

We do not know if eating food or drinking water containing acrolein affects your health. However, animals that swallowed acrolein had stomach irritation, vomiting, stomach ulcers, and bleeding. No one knows if breathing or eating acrolein or spilling it on your skin causes birth defects, affects your ability to have children, or causes cancer. The Department of Health and Human Services (DHHS) has not classified acrolein as to its carcinogenicity. International Agency for Resarch on Cancer (IARC) has determined that acrolein is not classifiable as to carcinogenicity in humans. The EPA has stated that the potential carcinogenicity of acrolein cannot be determined based on an inadequate database. For further information on the health effects of acrolein in animals and humans, see Chapters 2 and 3.

1.6 HOW CAN ACROLEIN AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Acrolein is very irritating to the eyes, nose, throat, lungs, stomach, and skin. In general, children are not likely to be affected by acrolein more than adults. However, children who are sensitive to irritants in the air (such as children with asthma) may be more sensitive to lung irritation from acrolein.

In animal studies, ingestion of very large amounts of acrolein during pregnancy caused reduced birth weights and skeletal deformities in newborns. However, the levels causing these effects were often fatal to the mother.

More information on the effect of acrolein in children can be found in Section 3.7.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO ACROLEIN?

If your doctor finds that you have been exposed to substantial amounts of acrolein, ask whether your children might also have been exposed. Your doctor might need to ask your state health department to investigate.

Children are expected to be exposed to acrolein in the same ways that adults are exposed. Like adults, children may be exposed to unknown levels from inhaling second-hand tobacco smoke. Children's exposure from eating or touching contaminated soil is not likely to differ from that of adults, because acrolein evaporates quickly, does not move well in soil, and doesn't last long in the environment. You can reduce your family's exposure to acrolein by reducing their exposure to tobacco smoke, smoke from burning wood products or cooking oils and grease, and exhaust from diesel or gasoline vehicles.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ACROLEIN?

Tests have been developed that can measure acrolein or its breakdown products in blood or urine. These tests require specialized laboratory equipment and cannot be performed in a physician's office. These tests also cannot be used to determine whether or not you have been exposed to acrolein in the environment, because acrolein can be produced by the breakdown of other chemicals in the body. For more detailed information, see Chapters 3 and 7.

1.9 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. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic

Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

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 that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

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 provides it. Some regulations and recommendations for acrolein include the following:

The EPA

- has restricted the use of all pesticides containing acrolein and has also identified acrolein as a toxic waste.
- requires that companies that make, transport, treat, store, or dispose of acrolein comply with the regulations of a federal hazardous waste management program.
- has also proposed standards that limit the amount of acrolein put into publicly owned waste water treatment plants.
- requires that releases or spills of one pound or more be reported to the National Response Center.

The FDA has determined that levels of acrolein used to prepare modified food starch must not be more than 0.6%.

OSHA has set a limit of 0.1 ppm acrolein in workroom air to protect workers during an 8-hour shift over a 40-hour workweek. NIOSH recommends that the concentration in workroom air be limited to 0.1 ppm averaged over an 8-hour shift.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-888-42ATSDR (1-888-422-8737), by e-mail at atsdric@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ACROLEIN IN THE UNITED STATES

Acrolein is a reactive aldehyde primarily used as an intermediate in chemical manufacturing and as a biocide. It is used in the synthesis of many organic chemicals, as a biocide in agricultural and industrial water supply systems, in the manufacture of methionine (an animal feed supplement), as a warning agent (due to its pungent odor) in methyl chloride refrigerant, and as a component of chemical weapons. Acrolein can be formed in burning tobacco, wood, plastics, gasoline and diesel fuel, paraffin wax, and in the heating of animal and vegetable fats and oils at high temperatures. It is also found naturally in the body in very small amounts.

Because acrolein is formed naturally in the body as a product of lipid oxidation and the metabolism of α-hydroxyamino acids, the general population is endogenously exposed to small amounts of acrolein. However, the general population is not likely to receive high exposures of acrolein. Individuals likely to receive the highest exposures include smokers and those inhaling second-hand smoke, persons in close proximity to sources of wood and plastic smoke, including those in the forest products and firefighting communities, and populations living or working in areas of dense automotive traffic. The predominant route of environmental exposure would be inhalation of smoke or automotive exhaust. No significant acrolein exposure is expected from ingestion of drinking water or from dermal contact during bathing or showering.

Acrolein is expected to volatilize rapidly from surface water and soil. Degradation in water, soil, and air occur quickly. Thus, environmental persistence is not expected. When applied to surface water as an herbicide, acrolein may persist for up to 6 days. It has been detected in 31 of 1,662 National Priority List (NPL) sites. It has not been found as a contaminant in drinking water. Acrolein has been detected in very low levels in rainwater in Los Angeles, California, a high-smog area. Average acrolein concentrations measured at various monitoring stations ranging from 0.5 to 3.186 ppbv (parts acrolein per billion parts of air by volume). The concentrations of acrolein in indoor air range from <0.02 to 12 ppb in residential homes. Acrolein concentrations are found to be typically higher in indoor air when comparing paired indoor/outdoor samples taken at a site. A burned cigarette has been measured to generate 0.06–0.22 mg

of acrolein, which may result in a variable and significant inhaled concentration for the smoker or by stander by increasing the concentration of acrolein in the air of a typical room by 0.4–2 ppb.

With the exception of smoking, children and adults are expected to be exposed to acrolein by the same routes of exposure. Like adults, however, children may be exposed to unknown levels of acrolein from inhaling second-hand tobacco smoke. Since acrolein is volatile, ineffectively transported in soil, and nonpersistent in the environment, children's dermal exposure from soil contact or ingestion is not likely to differ from adults.

See Chapter 6 for detailed information regarding concentrations of acrolein found in environmental media.

2.2 SUMMARY OF HEALTH EFFECTS

Acrolein can exert toxic effects following inhalation, oral, and dermal exposures. It is a potent irritant to the mucous membranes. At high concentrations, it can also cause irritation to skin. As such, its toxicity is exerted at the point of contact with tissues. Signs and symptoms resulting from inhalation exposure to airborne acrolein may include irritation of the nose, throat and lungs, pulmonary edema, lung hemorrhage, and death. The nasal tissues appear to be the most sensitive target of inhalation exposure, with onset of noticeable irritation occurring in seconds (0.3 ppm). Higher airborne concentrations of acrolein (2–5 ppm) result in increasingly severe manifestations of irritation over the entire respiratory tract. Oral acrolein exposure may result in gastrointestinal discomfort, vomiting, and stomach ulceration and/or hemorrhage. The stomach epithelium appears to be the most sensitive target for oral exposure (0.75 mg/kg). Higher concentrations of ingested acrolein have primarily resulted in increasingly severe irritation effects in the stomach (2 mg/kg and higher). Dermal exposure to acrolein vapors or liquids may cause stinging of the eyes, lacrimation, and reddening, ulceration, or necrosis of the skin (10% acrolein solution). The eye appears to be the most sensitive target for dermal exposure (0.3 ppm). Histological changes in respiratory and gastrointestinal epithelium have been observed from both inhalation and oral exposures, respectively. Changes in body and organ weights, hematology, and serum biochemistry, as well as developmental effects such as skeletal malformations and reduced weight of offspring, have been observed in animals. Some of these effects are believed to be secondary effects of gastrointestinal and/or respiratory tract irritation (i.e., loss of appetite and weight loss due to gastrointestinal irritation). Similar effects appear to result from similar exposure levels across durations of inhalation exposures. *In vitro* studies have shown acrolein to be weakly mutagenic, capable of interfering with DNA repair

mechanisms. The evidence for the carcinogenicity of acrolein is equivocal, with a significant tumor incidence found in a single animal drinking water study. The findings of this study were challenged by an independent pathology working group. Another well-designed cancer bioassay in rats orally-gavaged at lower doses failed to detect significant increases in cancer incidence. The Department of Health and Human Services (DHHS) has not classified acrolein as to its carcinogenicity. International Agency for Research on Cancer (IARC) has determined that acrolein is not classifiable as to carcinogenicity in humans. The EPA has stated that the potential carcinogenicity of acrolein cannot be determined based on an inadequate database.

The following sections discuss significant effects resulting from exposure to acrolein in greater detail: eye irritation, respiratory, and gastrointestinal.

Eye Irritation. Acrolein vapor or liquid causes adverse ocular effects through simple point-of-contact irritation. At low airborne levels (0.3 ppm), ocular irritation is perceived as rapid-onset mild to moderate stinging of the eyes accompanied by increased blinking. Lacrimation occurs at higher levels (0.81 ppm), with an increase in severity of irritant sting. At low levels of vapor exposure, humans appear to adapt to ocular irritation, as volunteers exposed to a constant level of acrolein vapors for 60 minutes reported increasing irritation of the eyes up to 40 minutes, but reported no further increase in discomfort thereafter. Dogs and monkeys appear to be more sensitive than rodents to acrolein, as evidenced by lacrimation and blinking or closing of the eyes during intermediate-duration exposures to 3.7 ppm; however, no observable ocular changes were reported in guinea pigs and rats exposed for the same duration. It is not known at what exposure level acrolein causes structural damage to the eye, as no histological evaluation of the eye following acrolein exposure has been conducted.

Respiratory Effects. Acrolein may affect the entire respiratory tract, from the nasal epithelium to the alveolar spaces. The variety and severity of effects and depth of the respiratory tract to which effects extend increases as exposure level increases. Nasal irritation appears to be the most sensitive respiratory effect, based on reported irritation in humans and animals and cellular changes observed in animals. Rapid onset of nose and throat irritation and a reduction in breathing rate (believed to be a protective measure triggered by nose irritation) was reported by volunteers acutely exposed to levels (0.3 ppm); mild nasal epithelial dysplasia, necrosis, and focal basal cell metaplasia have been reported in rats at similar concentrations (0.25 ppm). Respiratory irritation was observed in animals as evidenced by decreased respiratory rates in mice and rats exposed to 1–3 ppm. Higher acute inhalation exposure levels (2–5 ppm) have resulted in more severe effects in animals, including epithelial hyperplasia, inflammation, and

moderate to severe histological alterations of the nasal, tracheal, and bronchial epithelium, bronchial epithelial destruction, pulmonary edema, and lung hemorrhage have been seen in mice, rats, and guinea pigs. Four human case reports of massive acute acrolein inhalation exposures, either occupationally or from heated cooking fats, list similar effects, including high fever, dyspnea, coughing, foamy expectoration, cyanosis, pulmonary edema, and death (concentrations unknown). Observed effects following intermediate- and chronic-duration exposures to acrolein (1–3 ppm) include histological alterations and inflammation across the entire respiratory tract of rats, monkeys, guinea pigs, dogs, rabbits, and hamsters. Respiratory effects seem to be similar in type of effect and severity across species and exposure duration.

Gastrointestinal Effects. The irritation of gastrointestinal mucosa appears to be the primary effect of oral exposure to acrolein. Human data for oral exposures are not available. The clinical signs of gastrointestinal effects in animals are similar and dose-related across species and acute and intermediate exposures, although possible adaptation to irritating effects may occur during chronic exposures. Effects of increasing severity include vomiting, epithelial hyperplasia, ulceration, hemorrhage, and edema of the stomach mucosa. There are little data for low-level (<2 mg/kg/day) acute doses. Acute and intermediate exposure effects of high doses (4–25 mg/kg) in mice, rats, and rabbits include severe mucosal inflammation ulceration, focal hemorrhage, and edema. Effects from low, intermediate-duration doses of 1.25 mg/kg/day in mice and 2.5 mg/kg/day in rats resulted in glandular and forestomach squamous epithelial hyperplasia, respectively. Conversely, chronic dosing levels of 2–4.5 mg/kg/day produced no significant gross or histopathological effects in rats, mice, or dogs. The reported differences in gastrointestinal sensitivity are not well understood; however, study differences in dose volumes may play a role. Dogs chronically given acrolein doses by capsule as low as 0.5 mg/kg/day vomited significantly through the first 4 weeks of exposure, but appeared to adapt as vomiting incidence was reduced thereafter. Data are not available to determine if an adaptive effect for chronic oral exposures would be observed at higher dose levels.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for acrolein. 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 MRL of 0.003 ppm has been derived for acute-duration inhalation exposure (14 days or less) to acrolein.

Studies in both humans and animals have reported acute effects of airborne acrolein. Observed effects include nasal irritation, discomfort, and reduction in respiratory rate in humans (Weber-Tschopp et al. 1977), reduction in respiratory rate in mice (Buckley et al. 1984; Kane and Alarie 1977) and rats (Cassee et al. 1996), histological changes in nasal epithelium of rats and mice (Cassee et al. 1996; Nielsen et al. 1984; Steinhagen and Barrow 1984), and reduction in bactericidal activity (as reflected by macrophagic clearance of *Klebsiella pneumoniae* bacteria) in mice (Aranyi et al. 1986). More severe observed effects include high fever, dyspnea, coughing, foamy expectoration, cyanosis, tracheal and alveolar epithelial destruction, pulmonary edema, lung hemorrhage, and possible death in humans, mice, rats, guinea pigs, hamsters, and dogs (Buckley et al. 1984; Catilina et el. 1966; Champeix et al. 1966; Dahlgren et al. 1972; Hales et al. 1988; Kilburn and Mackenzie 1978; Murphy et al. 1964; Skog 1950).

A reduction in bactericidal activity in rat lungs was observed at 0.1 ppm (Aranyi et al.1986), the lowest lowest-observed-adverse-effect level (LOAEL) identified, and at 3 ppm (Astry and Jakab 1983). The biological significance of this finding is unclear. Irritation of the nasal epithelium of rats exposed to 0.25 ppm resulted in mild disarrangement and necrosis of nasal epithelium (Cassee et al. 1996). Animals in the same study exposed to 0.67 ppm exhibited focal basal cell metaplasia, reduced epithelial glutathione reductase activity, cellular disarrangement, necrosis, and cell proliferation of the nasal respiratory epithelium. Mice and rats were observed to exhibit decreased respiratory rates following

exposures of 1–3 ppm (Kane and Alarie 1977; Nielsen et al. 1984; Steinhagen and Barrow 1984). Severe irritation and lung hemorrhage were observed in rats exposed to 130 ppm (Skog 1950). Death occurred in rats exposed to acrolein levels ranging from 130 to 327 ppm for 30 and 10 minutes, respectively (Catilina et al. 1966; Skog 1950).

Nasal irritation in humans has been observed at levels similar to those seen in animals. Weber-Tschopp et al. (1977) exposed volunteers for 40 minutes to gradually increasing levels of acrolein vapors. At the end 15 minutes, exposure levels were approximately 0.26 ppm. Volunteers scored irritancy as "a little" or "medium", which was statistically different from controls. However, the changing concentrations of acrolein made it difficult to fix the duration or level of exposure that was actually responsible for the onset of significant irritation. In another test reported in Weber-Tschopp et al. (1977), volunteers exposed to 0.3 ppm acrolein for 60 minutes scored nose and throat irritation as "a little irritating" by 40 minutes into the exposure. A decrease in respiratory rate was also observed. This test, with a fixed exposure level and duration, was used as the basis for an acute duration inhalation MRL, providing a LOAEL of 0.3 ppm.

An acute duration inhalation MRL of 0.003 ppm was derived using the LOAEL of 0.3 ppm for nasal and throat irritation and decreased respiratory rate in humans. The LOAEL of 0.3 ppm was divided by an uncertainty factor of 100 (10 for using a LOAEL and 10 for human variability).

While Aranyi et al. (1986) reported a LOAEL of 0.1 ppm for reduced bactericidal activity in rats, the toxicological significance of this finding is unclear. Cassee et al. (1996) reported a LOAEL of 0.25 ppm, which was very similar to the human LOAEL of 0.3 ppm. This being the case, the human-derived data were deemed preferable for the basis of the MRL, eliminating the introduction of uncertainty from inter-species extrapolation.

- An MRL of 0.00004 ppm has been derived for intermediate-duration inhalation exposure (15–364 days) to acrolein.

No data were available for intermediate-duration exposure of humans to acrolein. Exposures to airborne acrolein concentrations between 0.4 and 5.0 ppm for up to 180 days caused a continuum of histological alterations, inflammation, and severe tissue destruction across the entire respiratory tract of rats, rabbits, guinea pigs, and monkeys (Costa et al. 1986; Feron et al. 1978; Kutzman et al. 1984, 1985; Lyon et al. 1970). Effects in the deeper respiratory tract became more severe at the 3–5 ppm exposure levels. Effects included tracheal epithelial metaplasia in hamsters (Feron et al. 1978), epithelial dysplasia in rats

(Leach et al. 1987), squamous lung epithelial metaplasia in rats (Kutzman et al. 1985), tracheal metaplasia and bronchial necrosis in rats (Feron et al. 1978; Kutzman et al. 1985), pulmonary edema in rats (Costa et al. 1986), and lung hemorrhage in monkeys (Lyon et al. 1970).

The most sensitive effect for intermediate-duration inhalation appears to be nasal epithelial metaplasia and bronchial inflammation. These effects were observed in rats at 0.4 ppm (Feron et al. 1978; Kutzman et al. 1984). Lung inflammation was seen in monkeys and guinea pigs at 0.7 ppm (Lyon et al. 1970). At 1–1.4 ppm, bronchiolar, lung, and liver inflammation were observed in guinea pigs, hamsters, and rats (Feron et al. 1978; Kutzman et al. 1985; Lyon et al. 1970). At 1.4–1.8 ppm, lung and tracheal hyperplasia was seen in rats and monkeys (Costa et al. 1986; Lyon et al. 1970). Lung hemorrhage and decreased weight gain occurred in monkeys at 3.7 ppm (Lyon et al. 1970). Increased brain weight, tracheal squamous metaplasia, bronchial necrosis, and lung edema were observed in rats at 4 ppm (Costa et al. 1986; Kutzman et al. 1985). Monkeys and rats died at 3.7–4 ppm (Kutzman et al. 1985; Lyon et al. 1970).

The intermediate-duration inhalation MRL was based on the lowest identified LOAEL of 0.4 ppm for nasal metaplasia in rats (Feron et al. 1978). This study compared the effects of a 13-week exposure of rats, rabbits, and hamsters for 6 hours/day, 5 days/week to 0.4, 1.4, and 4.0 ppm acrolein. The rat appeared to be the most sensitive species in the study, exhibiting more severe histological changes across the respiratory tract than the other species. Though bronchiolar inflammation was also observed in rats at 0.4 ppm (Feron et al. 1978), structural changes in the nasal epithelium appear to be a more sensitive effect, as such changes have been observed in lower, acute inhalation exposures of rats (Cassee et al. 1996). Structural changes to lung cells have not been observed in rats below 1.4 ppm (Costa et al. 1986). For these reasons, the LOAEL of 0.4 ppm for nasal metaplasia in rats was chosen as the most sensitive end point for the derivation of an intermediate-duration inhalation MRL.

The intermediate-duration inhalation MRL of 0.00004 ppm was derived by dividing the human equivalent LOAEL ($LOAEL_{HEC}$) of 0.012 ppm by 300 (10 for using a LOAEL, 3 for species extrapolation using dosimetric adjustment, and 10 for human variability). The duration-adjusted LOAEL ($LOAEL_{ADJ}$) was calculated as follows:

$LOAEL_{ADJ}$ = 0.4 ppm x 6 hours/24 hours x 5 days / 7 days = 0.071 ppm

Dosimetric adjustments for species differences for a category 1 gas in rats and humans (EPA 1994) resulted in a regional gas dose ratio for the extrathoracic region ($RGDR_{ET}$) of 0.17. The $LOAEL_{ADJ}$ was multiplied by the $RGDR_{ET}$ to derive the $LOAEL_{HEC}$ of 0.012 ppm as follows:

$LOAEL_{HEC} = LOAEL_{ADJ} \times RGDR = 0.071 \times 0.17 = 0.012$ ppm

No chronic-duration MRL for inhalation of acrolein was derived due to an inadequate database. An 18-month study with rats (Le Bouffant et al. 1980) reported epithelial hyperplasia. However, the study involved a 1-hour exposure to a very high concentration (8 ppm) of acrolein in which acrolein-treated animals were compared histologically to animals exposed daily to cigarette smoke rather than controls. The study is unclear as to whether this effect was attributable to the animals' exposure to acrolein or cigarette smoke.

Oral MRLs

No human oral exposure data for any exposure duration were available. Oral exposure studies in rabbits (Parent et al. 1993) and rats (Sakata et al. 1989) exposed to 4 and 25 mg/kg/day, respectively, reported severe stomach ulceration and edema, and death. Pregnant rabbits given 2 mg/kg/day by gavage exhibited a transient decrease in body weight which rebounded completely in 3 days (Parent et al. 1993). The lowest acute LOAEL identified was capsule dosing of 0.5 mg/kg/day in dogs, which resulted in vomiting shortly after dosing for the first 4 weeks of a chronic study. This effect was transient and may have been impacted by the capsule sub-route of administration. Further, statistical significance of the vomiting incidence was not determined. Since a higher no-observed-adverse-effect level (NOAEL) of 0.75 mg/kg/day was identified in a well-conducted intermediate-duration oral gavage study (NTP 1995), no acute-duration MRL for ingestion of acrolein was derived.

- An MRL of 0.008 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to acrolein.

No studies were located for intermediate-duration oral exposure to acrolein in humans. The limited number of animal studies identified for this exposure duration reported similar effects on the gastrointestinal and respiratory mucosa from oral and inhalation exposures, respectively. Forestomach and glandular squamous epithelial hyperplasia was seen in rats and mice, respectively, given 1.25 mg/kg/day by gavage (NTP 1995). Forestomach and glandular stomach hyperplasia, ulcers, and glandular stomach hemorrhage were observed in rats given 3 mg/kg/day (Parent et al. 1992c). Stomach

ulceration and hemorrhage was observed in rats given 5–5.4 mg/kg/day (King 1984; NTP 1995). Labored breathing and increased mortality were seen in rats given 6 mg/kg/day (Parent et al. 1992c). Stomach necrosis and hemorrhage were observed in mice and rats given 10 mg/kg/day (NTP 1995).

The 13-week gavage toxicity study in rats and mice (NTP 1995) served as the basis for deriving an intermediate-duration oral MRL. In this study, rats were administered 0.75, 1.25, 2.5, 5, and 10 mg/kg/day by gavage for 13 weeks, while mice were given 1.25, 2.5, 5, 10, and 20 mg/kg for the same duration. Glandular stomach lesions were observed in male and female mice gavaged with 10 and 20 mg/kg/day, respectively. Glandular stomach lesions were observed in mice given 10 mg/kg/day. Forestomach squamous epithelial hyperplasia was observed in male and female rats gavaged with 2.5 and 1.25 mg/kg/day, respectively. No effect was observed in female rats given 0.75 mg/kg/day. Although humans do not have a forestomach, this study provides an example of gastrointestinal mucus membrane irritation. Similar irritative effects are expected in humans. This effect represented the highest identified NOAEL associated with the lowest LOAEL in a well-designed study and served as the basis for the intermediate oral MRL.

The intermediate-duration oral MRL of 0.008 mg/kg/day was derived by dividing the NOAEL of 0.75 mg/kg/day for forestomach squamous epithelial hyperplasia in rats by a factor of 100 (10 for species extrapolation and 10 for human variability).

No chronic-duration oral MRL was derived for acrolein due to an inadequate database. Chronic gavage studies in which rats were dosed with up to 2.5 mg/kg/day for 24 months (Parent et al. 1992a), mice were gavage dosed with up to 4.5 mg/kg/day for 18 months (Parent et al. 1991), and dogs were gavage dosed with up to 2 mg/kg/day for 12 months (Parent et al. 1992b) all failed to produce significant gross or histopathological changes as have been observed in other studies of the same species at lower dose levels (NTP 1995). Body weight decreases were significant in male mice and rats (Parent et al. 1991, 1992c); however, the magnitude of body weight change could not be determined since variation between treatment groups was not reported. The Parent et al. (1992b) rat study also reported significantly depressed serum creatinine phosphokinase levels. However, the significance of this finding is unknown. Decreased survival (increased mortality) was observed in rats and mice dosed with 0.5 and 4.5 mg/kg/day, respectively (Parent et al. 1991, 1992a), but no explanation for the mortality was given.

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 acrolein. 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 (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. 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.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of acrolein are indicated in Table 3-2 and Figure 3-2.

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

3.2.1.1 Death

The only available information regarding lethal effects in humans after inhalation exposure to acrolein was provided by Gosselin et al. (1979), who described the cases of 2- and 4-year-old boys exposed for 2 hours to acrolein-containing smoke from an overheated fryer. The 2-year-old boy died 24 hours later of asphyxia. The data from this case report must be considered qualitative only, since smoke components other than acrolein may have contributed to the injury.

The data in experimental animals clearly indicate that respiratory toxicity is a primary cause of acrolein lethality following inhalation and show an inverse relationship between the exposure concentration and the time it takes for death to occur after acute-duration exposures. Exposure of rats to airborne concentrations of acrolein of 100–40,000 ppm for short periods of time (<l hour) caused death ranging from minutes to 11 days (Catilina et al. 1966; Crane et al. 1986; Skog 1950). Death was attributed to obstruction of trachea and bronchi, pulmonary edema, or hemorrhage. Single and repeated exposures to

3–4 ppm acrolein caused death in rats and monkeys before the 10th day of exposure (Carpenter et al. 1949; Kutzman et al. 1981, 1984, 1985; Lyon et al. 1970). Respiratory congestion was observed in the monkeys. Animal data regarding cause of death is in good agreement with observations made in humans after accidental exposure (Gosselin et al. 1979). Reliable NOAELs and LOAELs for lethality in experimental animals following inhalation exposure to acrolein are presented in Table 3-1 and Figure 3-1.

3.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, musculoskeletal, renal, or dermal effects in humans or animals after inhalation exposure to acrolein. 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.

Respiratory Effects. Champeix et al. (1966) reported a case of a 36-year-old male who was accidentally exposed to unknown concentrations of acrolein vapors in the workplace for <1 day (duration assumed). Observed symptoms included high fever, dyspnea, coughing, foamy expectoration, and cyanosis. Eighteen months after the exposure, the chronic pneumopathy and dyspnea persisted, although no information was reported regarding any pre-existing pulmonary conditions or possible lifestyle factors (i.e., smoking) that may have impacted the diagnosis.

Volunteers exposed to increasing levels of acrolein vapors for 35 minutes reported statistically significant nose irritation at 0.26 ppm, throat irritation at 0.43 ppm, and a decrease in respiratory rate at 0.60 ppm (Weber-Tschopp et al. 1977). No statistically significant difference was observed between controls and subjects exposed to 0.17 ppm. In the same study, constant exposure to 0.3 ppm acrolein for 40 minutes resulted in reports of mild nose irritation shortly after onset of exposure, while throat irritation was reported after 10 minutes. Severity of irritation was subjectively scored as “not at all’ to “a little”. A 20% decrease in respiratory rate was also observed. The significance of the decrease in respiratory rate is not clear, but in animals, particularly rodents, it is considered to represent a reflex response to protect the respiratory tract from toxicants (Alarie 1973). Based on the nose and throat irritation and a decrease in respiratory rate in humans exposed to acrolein, an acute-duration MRL of 0.003 ppm has been calculated from the LOAEL of 0.3 ppm (Weber-Tschopp et al. 1977).

Acute exposure of mice, rats, and guinea pigs to concentrations of 0.3–17 ppm acrolein for several minutes induced vasodilation (Morris et al. 1999), as well as an increase in airflow resistance and a reflex decrease in respiratory rate by activation of the sensory nerve endings in the nasal mucosa (Alarie 1973;

Table 3-1 Levels of Significant Exposure to Acrolein - 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	Monkey	6 wk 5d/wk 8hr/d				3.7 (1/9 died)	Lyon et al. 1970	Death occurred 9 days into exposure.
2	Rat (Wistar)	1 d 10min/d				327 M (LC 50)	Catilina et al. 1966	Group size and incidence rates not reported.
3	Rat (NS)	1 d 30min/d				130 (28/48 died)	Skog 1950	
Systemic								
4	Human	1 d 1hr/d	Resp		0.3[b] (decreased resp rate, nose and throat irritation)		Weber-Tschopp et al. 1977	

Table 3-1 Levels of Significant Exposure to Acrolein - 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
5	Rat (Wistar)	1x 4hr	Resp		1 M (Reduced levels of ascorbic acid, alpha-tocopherol, reduced glutathione, thiols, angiotensin -converting enzyme, lactase, lactase dehydrogenase, catalase and glutathione peroxidase activities. Increased levels of TBARS, conjugated dienes, superoxide dismutase activity.)	2 M (Desquamized and mononuclear cells, hyperemia, and emphysema.)	Arumugan et al. 1999	
6	Rat (Wistar)	6hr/day 3 d	Resp		0.67 F (nasal epithelial dyspalsia, moderate necrosis, desquamation, basal cell hyperplasia)		Cassee et al. 1996	
					1.4 F (nasal epithelial cell proliferation, reduced glutathione activity)			
					0.25 F (nasal epithelial dyspalsia, slight necrosis, desquamation, basal cell hyperplasia)			

Table 3-1 Levels of Significant Exposure to Acrolein - 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
7	Rat (Wistar)	1 d 10min/d	Resp			283 M (mucosal secretions, ciliary destruction, moderate laryngeal edema, scattered punctuate hemorrhaging)	Catilina et al. 1966	Group size and incidence rates not reported.
8	Rat (Fischer- 344)	1 x d 40 min	Resp		9.1 M (increased albumin in nasal lavage fluid)		Morris 1996	
9	Rat (Fischer- 344)	1 x d 50 min	Resp		2 M (vasodilation of upper resp tract)		Morris et al. 1999	
10	Rat	5 d 4hr/d	Hepatic		4 (decrease in relative liver weight)		Murphy et al. 1964	
			Bd Wt		4 (decreased bd wt)			
11	Rat	20-81 hr	Hepatic	1	2.1 (increase in liver weight)		Murphy et al. 1964	
12	Rat	9 d 4hr/d	Hepatic		3.9 (decrease in relative liver weight)		Murphy et al. 1964	
13	Rat	1 d 4hr/d	Resp		12 (severe resp tract irritation)		Murphy et al. 1964	

Table 3-1 Levels of Significant Exposure to Acrolein - 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
14	Rat	1 d 30min/d	Resp			130 (lung hemorrhage)	Skog 1950	
15	Mouse	5 d 6hr/d	Resp		1.7 (RD50, olfactory exfoliation erosion, ulceration, necrosis and squamous metaplasia)		Buckley et al. 1984	
16	Mouse	4 d 3hr/d	Resp		1.7 (RD50)		Kane & Alarie 1977	
17	Mouse (C57BL/6N)	1 x d 50 min	Resp		1.1 (increased airflow resitance)		Morris et al. 2003	
18	Mouse (C57BL/6N)	1 x d 10 min	Resp		1.3 (decreased breathing rate and airway resitance; increased respiratory pause)		Morris et al. 2003	
19	Mouse (C57BL/6N)	1 x d 10 min	Resp		0.3 (decreased breathing rate relative to non-diseased animals)		Morris et al. 2003	Compared effects in allergic airway-diseased and non-diseased animals
20	Mouse	1 d 30min/d	Resp		2.9 (RD50)		Nielsen et al. 1984	

Table 3-1 Levels of Significant Exposure to Acrolein - 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
21	Mouse (Swiss-Webster)	1 d 10min/d	Resp		1.03 (RD50)		Steinhagen & Barrow 1984	
22	Mouse (B6C3F1)	1 d 10min/d	Resp		1.41 (RD50)		Steinhagen & Barrow 1984	
23	Gn Pig	1 d 60min/d	Resp		17 (decreased resp rate)		Davis et al. 1967	
24	Gn Pig	1 d 2hr/d	Resp	0.6			Murphy et al. 1963	
Immuno/ Lymphoret								
25	Mouse	5 d 3hr/d			0.1 (decreased resistance to respiratory tract infection)		Aranyi et al. 1986	
26	Mouse	1 d 8hr/d			3 (decreased resistance to resp tract infection)		Astry & Jakab 1983	
INTERMEDIATE EXPOSURE								
Death								
27	Rat (Fischer- 344)	6 hr/d 5 d/wk 62 days				4 M (32/57 died)	Kutzman 1981	
28	Rat	62 d 5d/wk 6hr/d				4 (32/57 died)	Kutzman et al. 1985	

Table 3-1 Levels of Significant Exposure to Acrolein - 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
Systemic								
29	Rat	>60<180d 7d/wk 24hr/d	Resp		0.55 M (increased relative lung weight)		Bouley et al. 1975	
			Hepatic		0.55 M (increased relative liver weight)			
			Bd Wt		0.55 M (decreased bd wt gain)			
30	Rat (Wistar)	8 wk 10min/d	Resp			262 M (peribronchiolar hemorrhage; bronchial lumen obstruction)	Catilina et al. 1966	Group size and incidence rates not reported.
31	Rat (Fischer- 344)	62 d 5d/wk 6hr/d	Resp		1.4 (lung hyperplasia)	4 (lung edema and decreased function)	Costa et al. 1986	
			Bd Wt		4 (decreased bd wt gain)			
32	Rat	13 wk 5d/wk 6hr/d	Resp		0.4[c] (nasal squamous epithelial metaplasia)	4.9 (lung hemorrhage, necrotizing rhinitis)	Feron et al. 1978	
			Cardio	1.4	4.9 (increase in heart weight)			
			Hemato	4.9				
			Hepatic	4.9				
			Renal	1.4	4.9 (increase in kidney weight)			

Table 3-1 Levels of Significant Exposure to Acrolein - 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
33	Rat (Fischer- 344)	6 hr/d 5 d/wk 62 days	Resp		1.4	(bronchiolar epithelial hyperplasia, necrosis)			Kutzman 1981	
			Bd Wt		4 M	(decreased bd wt gains)				
34	Rat	62 d 5d/wk 6hr/d	Resp		0.4	(bronchiolar inflammation)	4	(squamous metaplasia)	Kutzman et al. 1984	
			Cardio	1.4	4	(increase in heart weight)				
			Hepatic	1.4	4	(increase in liver weight)				
			Bd Wt		4	(decreased bd wt gain)				
35	Rat	62 d 5d/wk 6hr/d	Resp		1.4	(bronchiolar inflammation)	4	(bronchiolar necrosis)	Kutzman et al. 1985	
			Cardio		4	(increase in heart weight)				
			Renal		4	(increase in kidney weight)				
			Bd Wt		4	(decrease in bd wt gain)				
36	Rat	3 wk 5d/wk 6hr/d	Resp		3	(epithelial dysplasia)			Leach et al. 1987	
			Bd Wt		3	(decreased bd wt gain)				

Table 3-1 Levels of Significant Exposure to Acrolein - 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
37	Rat	6 wk 5d/wk 8hr/d	Resp		0.7 (peribronchial inflammation)		Lyon et al. 1970	
			Renal	3.7				
			Dermal	3.7				
			Bd Wt		3.7 (decreased bd wt gain)			
38	Rat	90 d 7d/wk 24hr/d	Resp	1.8			Lyon et al. 1970	
			Cardio	1.8				
			Hemato	1.8				
			Hepatic	0.22	1 (focal necrosis)			
			Renal	1.8				
			Dermal	1.8				
			Bd Wt		1 (decreased bd wt gain)			
39	Rat	61 d 24hr/d	Hemato	0.32			Sinkuvene 1970	
			Bd Wt		0.32 (decreased bd wt gain)			
			Other	0.06				

Table 3-1 Levels of Significant Exposure to Acrolein - 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
40	Gn Pig (Hartley)	90 d 7 d/wk 24 hr/d	Resp	0.22	1	(pulmonary inflammation)			Lyon et al. 1970	
			Hemato	1.8						
			Hepatic	0.22	1	(liver inflammation)				
41	Gn Pig (Hartley)	6 wk 5d/wk 8hr/d	Resp		0.7	(peribronchial inflammation)			Lyon et al. 1970	
			Hemato	3.7						
			Renal	3.7						
			Dermal	3.7						
			Bd Wt	3.7						
42	Hamster	13 wk 5d/wk 6hr/d	Resp	0.4	1.4	(nasal epithelial inflammation)	4.9	(tracheal metaplasia, necrotizing rhinitis)	Feron et al. 1978	
			Cardio	1.4	4.9	(increased heart weight)				
			Hemato		4.9	(increases in PCV)				
			Hepatic	4.9						
			Renal	1.4	4.9	(increase in kidney weight)				
			Bd Wt		4.9	(decreased bd wt gain)				
			Other	1.4						

Table 3-1 Levels of Significant Exposure to Acrolein - 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
Immuno/ Lymphoret								
43	Rat	3 wk 5d/wk 6hr/d		3			Leach et al. 1987	
44	Rat	3 wk 5d/wk 6hr/d		3			Sherwood et al. 1986	
Neurological								
45	Monkey	90 d 7d/wk 24hr/d		1.8			Lyon et al. 1970	
46	Rat	62 d 5d/wk 6hr/d			4 (increase in brain weight)		Kutzman et al. 1984	
47	Hamster	13 wk 5d/wk 6hr/d		4.9			Feron et al. 1978	
Reproductive								
48	Rat (Fischer- 344)	6 hr/d 5 d/wk 62 days		4			Kutzman 1981	

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

b Used to derive an acute inhalation MRL of 0.003 ppm; dose divided by an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL).

c Used to derive an intermediate inhalation MRL of 0.00004 ppm; dose adjusted for duration and inter-species dosimetry of a category 1 gas, and divided by an uncertainty factor of 300 (3 for interspecies dosimetry, 10 for human variability and 10 for use of a LOAEL).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = Female; Gn pig = guinea pig; hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50%;LOAEL = lowest-observed-adverse-effect level; min = minute(s); NOAEL = no-observed-adverse-effect level; PCV = pact cell volume; RD50 = 50% decrease in respiratory rate; Resp = respiratory; wk = week(s)

Figure 3-1 Levels of Significant Exposure to Acrolein - Inhalation

Acute (≤14 days)

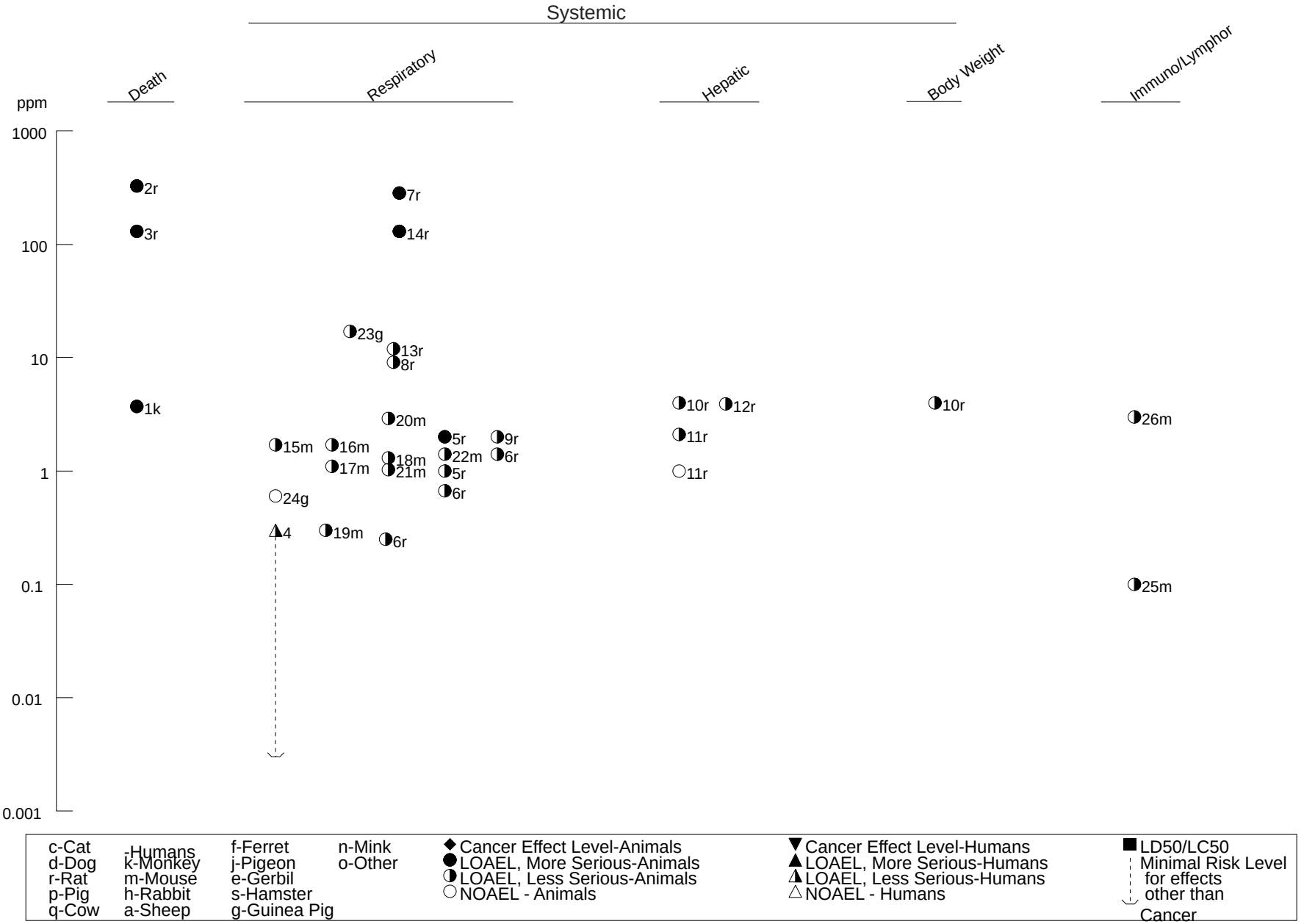


Figure 3-1 Levels of Significant Exposure to Acrolein - Inhalation

Intermediate (15-364 days)

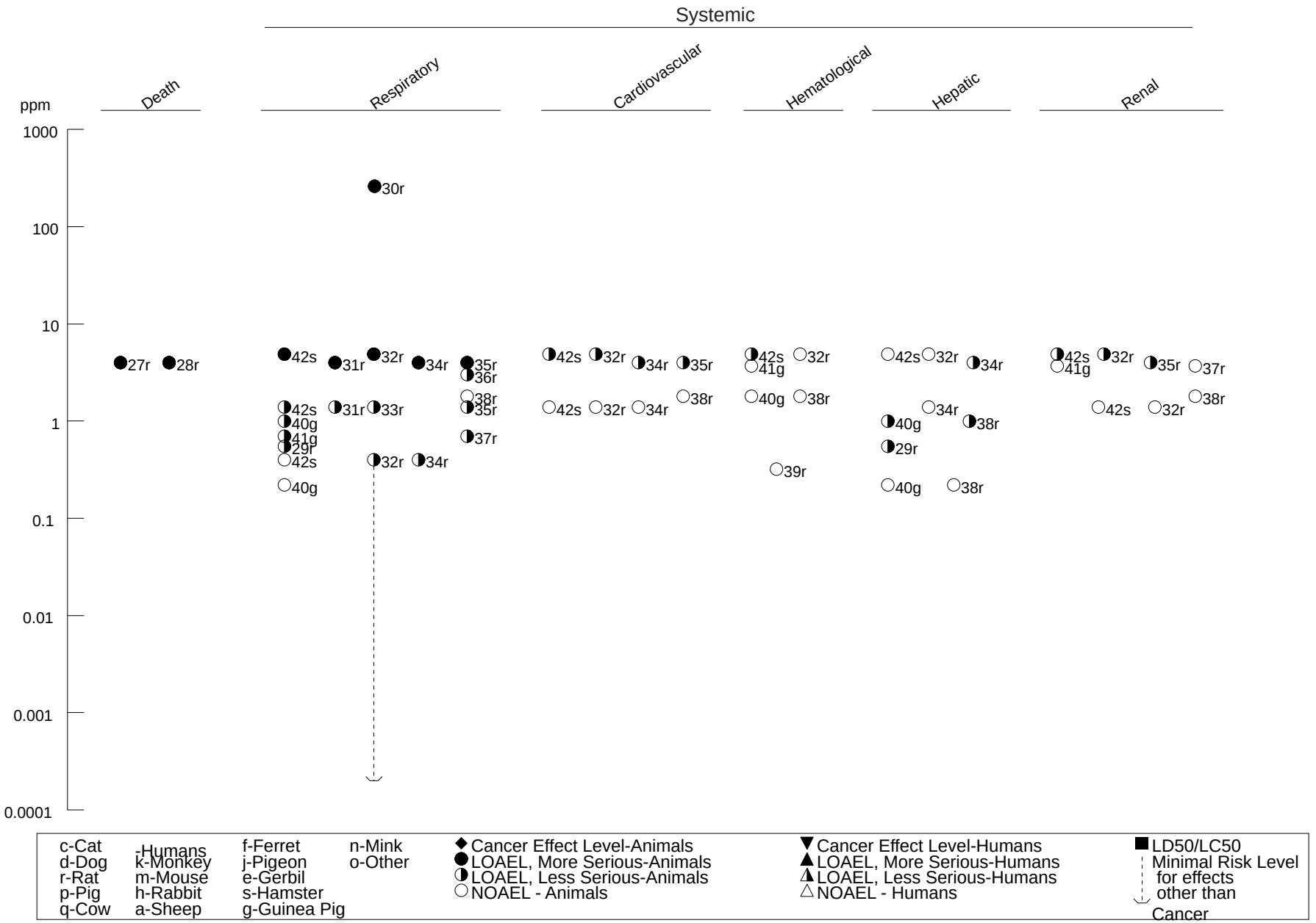
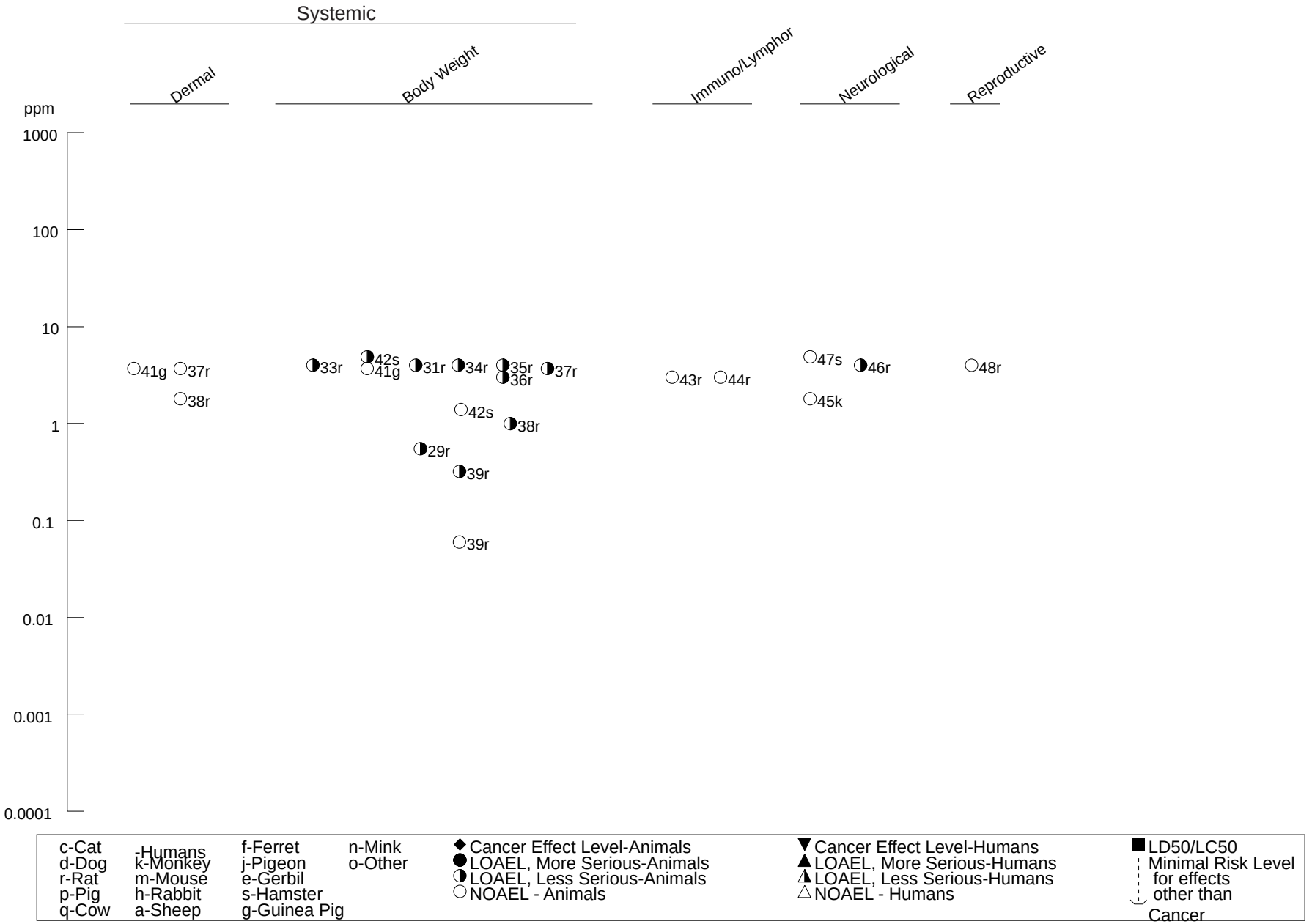


Figure 3-1 Levels of Significant Exposure to Acrolein - Inhalation

Intermediate (15-364 days)



Buckley et al. 1984; Davis et al. 1967; Kane and Alarie 1977; Leikauf et al. 1989a; Morris et al. 1999, 2003; Murphy et al. 1963; Nielsen et al. 1984; Steinhagen and Barrow 1984). Significantly decreased respiratory rates were observed in allergic airway-diseased mice compared to nondiseased mice exposed to 0.3 ppm acrolein for 10 minutes (Morris et al. 2003). Increased albumin levels were observed in nasal lavage fluid of rats exposed to 9.1 ppm for 40 minutes (Morris 1996). Olfactory exfoliation, erosion, ulceration, necrosis, and squamous metaplasia were observed in mice exposed to 1.7 ppm for 5 days (Buckley et al. 1984). Several indicators of oxidative stress were reported in rats exposed to 1 ppm for 4 hours (Arumugan et al. 1999), including reduced lung levels of ascorbic acid, alpha-tocopherol, reduced glutathione, thiols, angiotensin-converting enzyme, lactase, lactase dehydrogenase, catalase and glutathione peroxidase activities and increased levels of TBARS, conjugated dienes, and superoxide dismutase activity. In the same study, desquamized and mononuclear cells, hyperemia, and emphysema were observed in lung tissues following a 2-ppm exposure for 4 hours. Emphysema was not reported in any other acute-duration study. Rats exposed to 0.25–0.67 ppm for 6 hours on 3 consecutive days exhibited focal basal cell metaplasia, reduced epithelial glutathione reductase activity, slight to moderate epithelial necrosis, and disarrangement and cell proliferation of the nasal respiratory epithelium in a dose-dependent manner (Cassee et al. 1996). Biochemical alterations in the nasal mucosa were observed in rats exposed to 0.1–2.5 ppm, but the toxicological significance of this finding is unclear (Lam et al. 1985). Rat lungs exhibited significantly reduced glutathione, ascorbic acid, and α-tocopherol levels as well as glutathione peroxidase, catalase, and superoxide dismutase activity levels following 4-hour exposures to 1 or 2 ppm acrolein (Arumugam et al. 1999). Exposure to concentrations of 1.7–6 ppm induced epithelial hyperplasia, inflammation, and moderate to severe histological alterations of the nasal, tracheal, and bronchial epithelium of mice, rats, guinea pigs, hamsters, and dogs (Buckley et al. 1984; Feron et al. 1978; Kilburn and Mackenzie 1978; Murphy et al. 1964). Severe respiratory tract irritation was observed in rats exposed to 12 ppm for 4 hours (Murphy et al. 1964). Exposures as short as 5 minutes to >100 ppm acrolein resulted in bronchial epithelial destruction, pulmonary edema, and lung hemorrhage in rats, guinea pigs, and dogs (Catilina et al. 1966; Dahlgren et al. 1972; Hales et al. 1988; Skog 1950).

Intermediate-duration exposures to acrolein concentrations between 0.4 and 5.0 ppm for up to 180 days caused increased relative lung weights, as well as histological alterations, inflammation across the entire respiratory tract, and edema of rats (Bouley et al. 1975; Costa et al. 1986; Feron et al. 1978; Kutzman et al. 1981, 1984, 1985; Leach et al. 1987; Lyon et al. 1970), monkeys, guinea pigs, and dogs (Lyon et al. 1970), and rabbits and hamsters (Feron et al. 1978). Decreased pulmonary function was observed in rats exposed to 4 ppm for up to 62 days (Kutzman 1981). Daily 10-minute exposures of 262 ppm for 8 weeks resulted in peribronchial hemorrhage and bronchial lumen obstruction in rats (Catilina et al. 1966). Based

on the nasal epithelial metaplasia in rats exposed to acrolein, an intermediate-duration MRL of 0.00004 ppm has been calculated from the LOAEL of 0.4 ppm (Feron et al.1978).

In the chronic exposure study in rats (Le Bouffant et al. 1980), occasional emphysematous areas were reported in the alveoli after 18 months of exposure to 8 ppm acrolein for 1 hour daily, though the study is unclear as to whether this effect was attributable to the animal's exposure to acrolein, cigarette smoke, or a combination of the two.

The overall evidence from acute, intermediate, and chronic duration studies in experimental animals indicates that the respiratory system is a target for acrolein. While the entire respiratory tract may be affected by acrolein inhalation, the nasal epithelium appears to be more sensitive at lower exposures (<1 ppm), which is consistent with human perception of nasal irritation. The deeper respiratory regions (bronchiolar and alveolar regions) appear to be sensitive to higher exposure levels, with severe effects being observed from exposures of 100 ppm or higher. The available data do not suggest species differences in the respiratory toxicity of acrolein. Humans and animals appear to show similar low concentration effects (i.e., mild irritation). It should be noted, however, that rodents are obligate nose-breathers, while humans are mouth-breathers. As a result, the lower respiratory tract of rodents may not present as likely a target organ as that of humans.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following inhalation exposure to acrolein.

Nonspecific inflammatory lesions in the heart were reported in rats, dogs, monkeys, and guinea pigs after a continuous 90-day exposure to 0.22 ppm acrolein (Lyon et al. 1970). Also, an increase in relative heart weight was observed in hamsters and rats exposed to 4–5 ppm of acrolein (Feron et al. 1978; Kutzman et al. 1985). In both of these studies, dose-dependent changes in histology and gross pathology were only seen in the respiratory tract. Thus, the nonspecific cardiovascular effects may be secondary effects of acrolein on respiratory tissues.

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

No adverse hematological effects were observed in rats, guinea pigs, dogs, male hamsters, and monkeys exposed to 0.2–4.9 ppm of acrolein for an intermediate duration (Feron et al. 1978; Lyon et al. 1970).

However, statistically significant increased numbers of erythrocytes, hemoglobin, and lymphocytes were observed in female hamsters exposed at 4.9 ppm (Feron et al. 1978). The study authors did not discuss the implications of these changes. The toxicological significance of these changes, if any, is unknown.

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

Effects reported in rats after a 4-hour exposure to 8 ppm of acrolein included increases in alkaline phosphatase and tyrosine transaminase activities; however, these changes could represent adaptive responses (Murphy 1965; Murphy et al. 1964). Liver necrosis (minute foci without a specific pattern) was reported in rats and guinea pigs after intermediate-duration exposure to 1 ppm acrolein, but this effect was not found at a higher concentration (Lyon et al. 1970). Relative liver weight increases were observed in rats exposed to 0.55 ppm for 60–180 days (Bouley et al. 1975) and 4 ppm for 62 days (Kutzman 1984). An increase in relative liver weight was observed in rats exposed to 2.1 ppm for up to 81 hours (Murphy et al. 1964), while a decrease in relative liver weight resulted from exposure to 3.9 ppm for 5 or 9 days. No adverse liver effects were seen in hamsters, rabbits, monkeys, dogs, or guinea pigs exposed to ≤4.9 ppm acrolein (Feron et al. 1978).

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

Renal effects in guinea pigs, dogs, and monkeys were described as nonspecific (Lyon et al. 1970). An increase in amorphous material in the urinary sediment was observed in rats, hamsters, and rabbits after intermediate-duration exposure to 4.9 ppm acrolein (Feron et al. 1978). However, without further characterization of the sediment, the significance of this finding is unclear. Increases in kidney weights were seen in rats and hamsters exposed to 4–5 ppm for 9–13 weeks (Feron et al. 1978; Kutzman et al. 1985).

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to acrolein.

Increased adrenal weights (up to 20% relative to controls 100 hours after exposure) were reported in rats after acute exposures to 6.4 ppm for 4 hours (Murphy et al. 1964). However, the toxicological

significance of this difference cannot be ascertained since variation or statistical significance between groups was not reported.

Ocular Effects. Eye irritation appears to be the most sensitive effect of airborne acrolein. This effect, however, is point-of-contact limited and is independent of acrolein inhalation. Therefore, ocular effects are discussed in detail in Section 3.2.3, Dermal Exposure.

Body Weight Effects. In intermediate-duration studies, depressed body weight gains were reported in rats, hamsters, monkeys, and rabbits exposed to 0.32–4.9 ppm acrolein (Bouley et al. 1975; Feron et al. 1978; Kutzman et al. 1981, 1984, 1985; Leach et al. 1987; Lyon et al. 1970; Sinkuvene 1970). Significant differences in food consumption of rats were measured during exposure. However, food consumption increased significantly following cessation of exposure (Bouley et al. 1975). Anorexia was observed in rats exposed to 12 ppm for 4 hours (Murphy et al. 1964). It is not known why food consumption rates decreased during exposure. It is possible that animals minimized their activity levels in order to minimize respiration rates and, thus, relieve the discomfort of inhaling acrolein.

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after inhalation exposure to acrolein.

Short-term exposures to acrolein reduced bactericidal activity of the respiratory tract in experimental animals. Aranyi et al. (1986) observed a significantly lower removal by alveolar macrophages of *Klebsiella pneumoniae* bacteria from a 3-hour aerosol infection following a 5-day exposure to 0.1 ppm acrolein in mice. No difference was observed in rats for this same exposure/infection protocol (Sherwood et al. 1986). Similarly, 8-hour exposures to 3 and 6 ppm acrolein in mice showed a concentration-related reduction in clearance of *Staphylococcus aureus* from an 8-hour pulmonary infection; however, exposures to 8–10 ppm did not significantly add to the impairment of bactericidal activity (Astry and Jakab 1983). Rats exposed to 0.55 ppm for 10–26 days had significantly lower numbers of alveolar macrophages, but rats exposed for 60–180 days showed no significant difference in macrophage levels (Bouley et al. 1975). No statistically significant differences in mortality were observed in rats intravenously exposed to *Listeria monocytogenes* following a 3-week exposure to up to 3 ppm acrolein (Leach et al. 1987). These studies do not suggest that inhaled acrolein causes an immune system effect, but the reduction in removal of bacteria from the alveolar spaces may result from the destruction of functionality of alveolar macrophages present in the respiratory epithelium. The highest NOAEL values and all reliable LOAEL values for

immunological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to acrolein.

Springall et al. (1990) indicate that acrolein may induce release of peptides that could play a role in the physiological response to irritants. Concentrations of acrolein between 22 and 249 ppm for 10 minutes induced a dose-related decrease in substance P (a short-chain polypeptide that functions as a neurotransmitter or neuromodulator) and calcitonin gene-related peptide in nerve terminals innervating the trachea of rats (Springall et al. 1990). No change was seen in total nerve distribution and number or in vasoactive intestinal peptide. Likewise, substance P-mediated vasodilation of the rat upper respiratory tract was observed at 20 ppm, but not at 2–10 ppm, for 50 minutes (Morris et al. 1999).

In intermediate duration studies (Feron et al. 1978; Kutzman et al. 1984, 1985; Lyon et al. 1970), the neurological effects identified consisted of increases in the brain/body weight ratio and nonspecific inflammatory responses in sections of the brain (it is not clear from the original papers whether sections refer to anatomical areas or to histological preparations). These effects were observed in rats, guinea pigs, dogs, and monkeys at comparable concentrations of acrolein. The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and 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 acrolein.

Two studies were identified regarding the reproductive effects of inhaled acrolein. Bouley et al. (1975) exposed male and female rats to 0.55 ppm acrolein continuously for 26 days (3 days prior to mating and presumed gestational days 0 through 22) and reported that exposure did not affect the number of pregnancies or the number and weights of the fetuses. Although Bouley et al. (1975) examined the most relevant indices and an adequate number of animals were tested, the use of only one dose level limits the reproductive assessment derived from this study. Kutzman (1981) found no effect on the reproductive

fitness of rats exposed to 0.4–4 ppm for 62 days. The NOAEL value for reproductive effects in rats after an intermediate-duration exposure is 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 or animals after inhalation exposure to acrolein.

3.2.1.7 Cancer

No studies were located regarding carcinogenic effects in humans after inhalation exposure to acrolein.

Only two studies in animals were located that examined the carcinogenic potential of acrolein after inhalation exposure. Feron and Kruysse (1977) exposed hamsters to a single acrolein concentration of 4.0 ppm for 7 hours/day, 5 days/week for 52 weeks and found no evidence of respiratory tract tumors or tumors in other tissues and organs. However, this study is considered to be of too short duration to determine carcinogenicity. The maximum tolerable dose (MTD) of acrolein appears to have been achieved in this study, as indicated by the significant decrease in body weights of treated animals. Le Bouffant et al. (1980) exposed rats to 8 ppm acrolein for 1 hour/day, 7 days/week for 18 months and reported no evidence of tumors in the respiratory tract or in other tissues and organs. An MTD does not appear to have been achieved in this study due to the short daily duration of exposure.

3.2.2 Oral Exposure

3.2.2.1 Death

No studies were located regarding lethality in humans after oral exposure to acrolein.

The oral LD_{50} for rats was reported as 46 mg/kg, with a range of 39–56 mg/kg (Smyth et al. 1951). However, a single oral dose of 10–25 mg/kg in rats was lethal to over 40% of the animals (Draminski et al. 1983; Sakata et al. 1989; Sprince et al. 1979). Loss of reflexes occurred after 3 hours, and increased lethargy gradually led to death. Most of the animals died 3–8 hours after dosing (Sprince et al. 1979). Furthermore, increased maternal mortality was observed in rats treated with 10 mg/kg/day and in rabbits

treated with 4 mg/kg/day during gestational days 7–19 (King 1982; Parent 1993). No increase in deaths was observed in a two-generation reproductive study, in which rats were treated by gavage with 7.2 mg/kg/day (King 1984).

The overall survival rate was not affected in dogs exposed to 2 mg/kg/day by capsule dosing for 12 months (Parent 1992b). Decreased survival was, however, reported in male and female mice gavaged with 20 mg/kg/day for 13 weeks (NTP 1995), in male and female rats gavaged with 6 mg/kg/day for 93–149 days (Parent et al. 1992c), and in male mice gavaged with 4.5 mg/kg/day for 18 months (Parent et al. 1991). Survival of male and female rats was significantly decreased following intermediate-duration gavage exposure of 10 mg/kg/day for 13 weeks (NTP 1995). Chronically gavaged male mice and female rats receiving 4.5 and 0.5 mg/kg/day, respectively, experienced increased mortality, although the cause of mortality from the chronic exposure was not determined (Parent et al. 1991, 1992a). Chronic exposure of rats to 36 mg/kg/day or less of acrolein via the drinking water did not affect mortality (Lijinsky and Reuber 1987). It is difficult to explain the apparent contradiction in mortality observations between the chronic gavage studies (Parent et al. 1991, 1992a, 1992b) and the single chronic drinking water study (Lijinsky and Reuber 1987), especially since the cause of death is unknown. One possible explanation may be the slower delivery of the drinking water dose (presumably spread out over a day) compared to the bolus gavage dose. Another factor to be considered is the polymerization of acrolein, which would lower the effective acrolein concentration.

3.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, or ocular effects in humans after oral exposure to acrolein. However, studies were located regarding these end points in several species of animals. 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.

Respiratory Effects. Abnormal breathing was observed in rats gavaged with 10 mg/kg/day for 13 weeks (NTP 1995) and 6 mg/kg/day for 93–149 days (Parent et al. 1992c). No histopathological changes were observed in the respiratory systems of rats after intermediate-duration exposure to 7.2 mg/kg/day (King 1984). Similarly, no changes were observed during histopathological examination of respiratory tract tissues from rats (Parent et al. 1992a), mice (Parent et al. 1991), or dogs (Parent et al. 1992b) chronically exposed to 2.5, 4.5, or 2 mg/kg/day, respectively.

Table 3-2 Levels of Significant Exposure to Acrolein - 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	Gd 7-19 1x/d (GW)				10 (14/40 died)	King 1982	
2	Rat (Fischer- 344)	1xd				25 M (5/12 died)	Sakata et al. 1989	No controls were used.
3	Rat	1 x (G)				11.2 (LD 90)	Sprince et al. 1979	
Systemic								
4	Rat	Gd 7-19 1x/d (GW)	Bd Wt		6 (decreased bd wt gain)		King 1982	
			Other	3.6				
5	Rat (Fischer- 344)	1xd	Gastro			25 M (severe erosive hemorrhagic gastritis, multi-focal ulceration of forestomach and glandular stomach)	Sakata et al. 1989	No controls were used.
6	Rabbit (New Zealand)	1x/d Gd 7-19 (GW)	Bd Wt	0.75 F	2 F (transient depressed maternal bd wt gain)		Parent et al. 1993	
Reproductive								
7	Rat	Gd 7-19 1x/d (GW)		10			King 1982	

Table 3-2 Levels of Significant Exposure to Acrolein - 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
Developmental									
8	Rat	Gd 7-19 1x/d (GW)		6		10	(decreased litter weight, increased skeletal anomalies)	King 1982	
9	Rabbit (New Zealand)	1x/d Gd 7-19 (GW)		2 F				Parent et al. 1993	
INTERMEDIATE EXPOSURE									
Death									
10	Rat (Fischer- 344)	1/d 13 weeks (GW)				10	(17/20 died)	NTP 1995	
11	Rat (Sprague-Dawley)	1/d 93-149 d (GW)				6	(increased mortality)	Parent et al. 1992c	
12	Mouse (B6C3F1)	1/d 13 weeks (GW)				20	(20/20 died)	NTP 1995	

Table 3-2 Levels of Significant Exposure to Acrolein - 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
Systemic								
13	Rat	115 d 1x/d (GW)	Resp	7.2			King 1984	
			Cardio	7.2				
			Gastro	4	5.4 (stomach ulcerations)			
			Hemato	7.2				
			Musc/skel	7.2				
			Hepatic	7.2				
			Renal	7.2				
			Dermal	7.2				
			Bd Wt		7.2 (decreased bd wt in F0 generation)			
			Other	5.4				
14	Rat (Fischer- 344)	1/d 13 weeks (GW)	Resp			10 (abnormal breathing)	NTP 1995	
			Gastro	1.25 M 0.75[b] F	2.5 M (forestomach squamous epithelial hyperplasia)	5 M (glandular stomach hemorrhage)		
					1.25 F (forestomach squamous epithelial hyperplasia)	10 F (glandular stomach hemorrhage)		
						10 (forestomach necrosis and hemorrhage)		

Table 3-2 Levels of Significant Exposure to Acrolein - 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
15	Rat (Sprague-Dawley)	1/d 93-149 d (GW)	Resp			6 (rales, labored/irregular breathing, gasping, hyperpnia in F0 and F1 generations)	Parent et al. 1992c	
			Gastro		3 (forestomach and glandular stomach hyperplasia, ulcers)	3 (glandular stomach hemorrhage)		
			Renal		6 M (reddish-brown urine)			
			Bd Wt		6 M (decreased bd wt gains in F0 and F1 generations)			
16	Mouse (B6C3F1)	1/d 13 weeks (GW)	Gastro	1.25 F	1.25 M (glandular stomach squamous epithelial hyperplasia)	10 M (stomach necrosis and hemorrhage)	NTP 1995	
					2.5 F (glandular stomach squamous epithelial hyperplasia)	20 F (stomach necrosis and hemorrhage)		
			Hepatic		10 M (increased absolute and relative liver weight)			
Reproductive								
17	Rat	115 d 1x/d (GW)		7.2			King 1984	

Table 3-2 Levels of Significant Exposure to Acrolein - 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
18	Rat (Sprague-Dawley)	1/d 93-149 d (GW)		6			Parent et al. 1992c	
Developmental								
19	Rat (Sprague-Dawley)	1/d 93-149 d (GW)			6 (decreased pup bd wt)		Parent et al. 1992c	
CHRONIC EXPOSURE								
Death								
20	Rat (Sprague-Dawley)	1x/d 102 weeks (GW)				0.5 F (increased mortality)	Parent et al. 1992a	
21	Mouse (CD-1)	18 mo 7d/wk 1x/d (GW)				4.5 M (increased mortality)	Parent et al. 1991	
Systemic								
22	Rat (Sprague-Dawley)	1x/d 102 weeks (GW)	Resp	2.5			Parent et al. 1992a	
			Gastro	2.5				
			Hemato	2.5				
			Musc/skel	2.5				
			Hepatic	2.5				
			Endocr	2.5				
			Ocular	2.5				
			Bd Wt	2.5				

Table 3-2 Levels of Significant Exposure to Acrolein - 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
23	Mouse	18 mo 7d/wk 1x/d (GW)	Resp	4.5			Parent et al. 1991	
			Gastro	4.5				
			Hemato	4.5				
			Musc/skel	4.5				
			Hepatic	4.5				
			Endocr	4.5				
			Ocular	4.5				
			Bd Wt		4.5 M (decreased bd wt gain)			

Table 3-2 Levels of Significant Exposure to Acrolein - 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
24	Dog (Beagle)	365 d 1x/d (C)	Resp	2			Parent et al. 1992b	
			Gastro		0.5 (vomiting after daily dosing, incidence decreased after week 4)			
			Hemato		2 (decreased prothrombin time, decreased mean corpuscular volume and hemoglobin in females; these parameters increased in males)			
			Musc/skel	2				
			Hepatic	2				
			Renal	2 F				
			Endocr	2				
			Dermal	2				
			Ocular	2				
			Bd Wt	2				
Cancer								
25	Rat (Sprague-Dawley)	1x/d 102 weeks (GW)		2.5			Parent et al. 1992a	

Table 3-2 Levels of Significant Exposure to Acrolein - 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
26	Mouse	18 mo 7d/wk 1x/d (GW)		4.5			Parent et al. 1991	

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

b Used to derive an intermediate oral MRL of 0.008 mg/kg/day; based on a NOAEL of 0.75 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for human variability and 10 for species extrapolation).

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); F = Female; Gastro = gastrointestinal; Gd = gestational day; hemato = hematological; LD90 = lethal dose, 90% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; x = time(s); wk = week(s)

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

Acute (≤14 days)

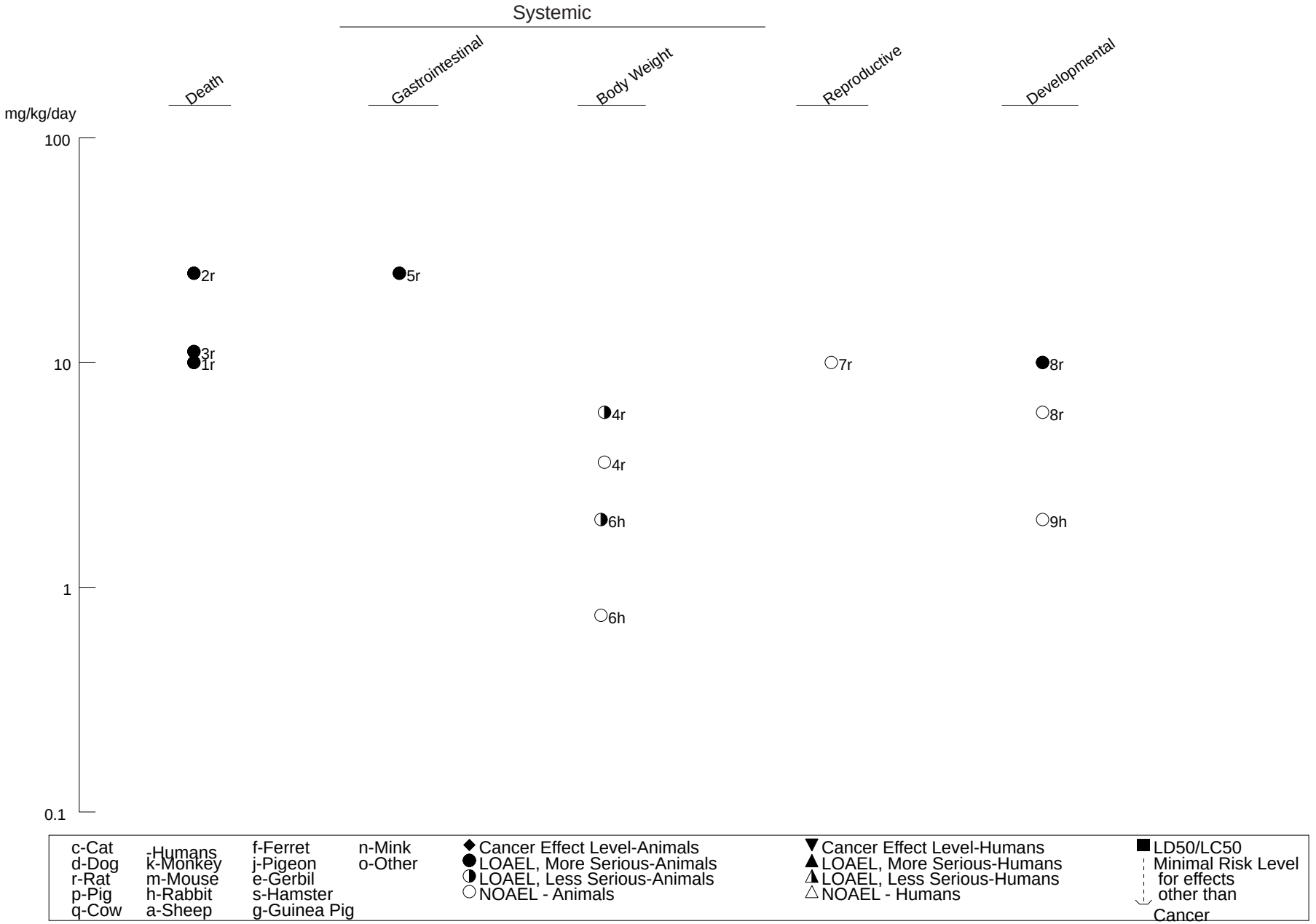


Figure 3-2 Levels of Significant Exposure to Acrolein - Oral

Intermediate (15-364 days)

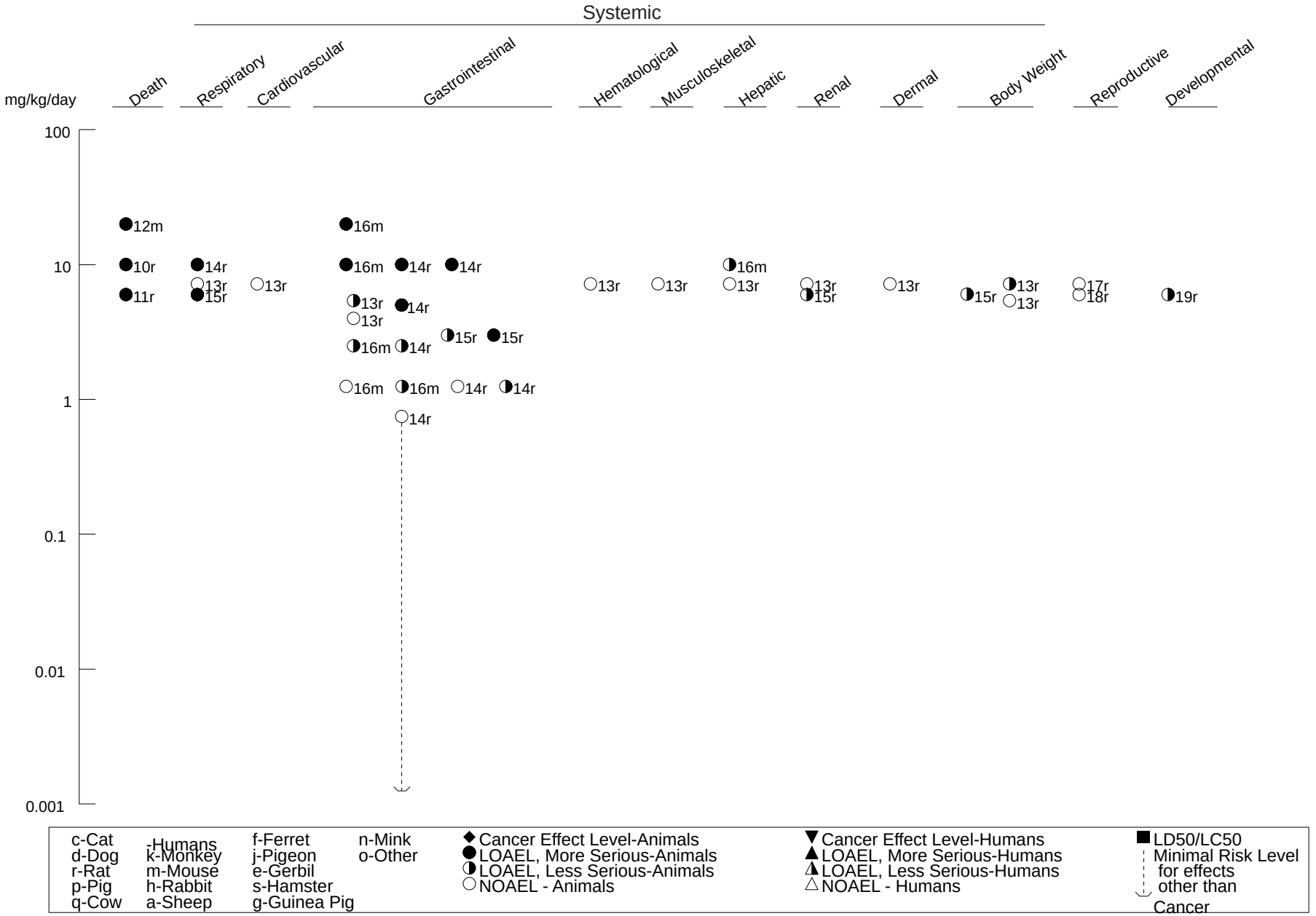
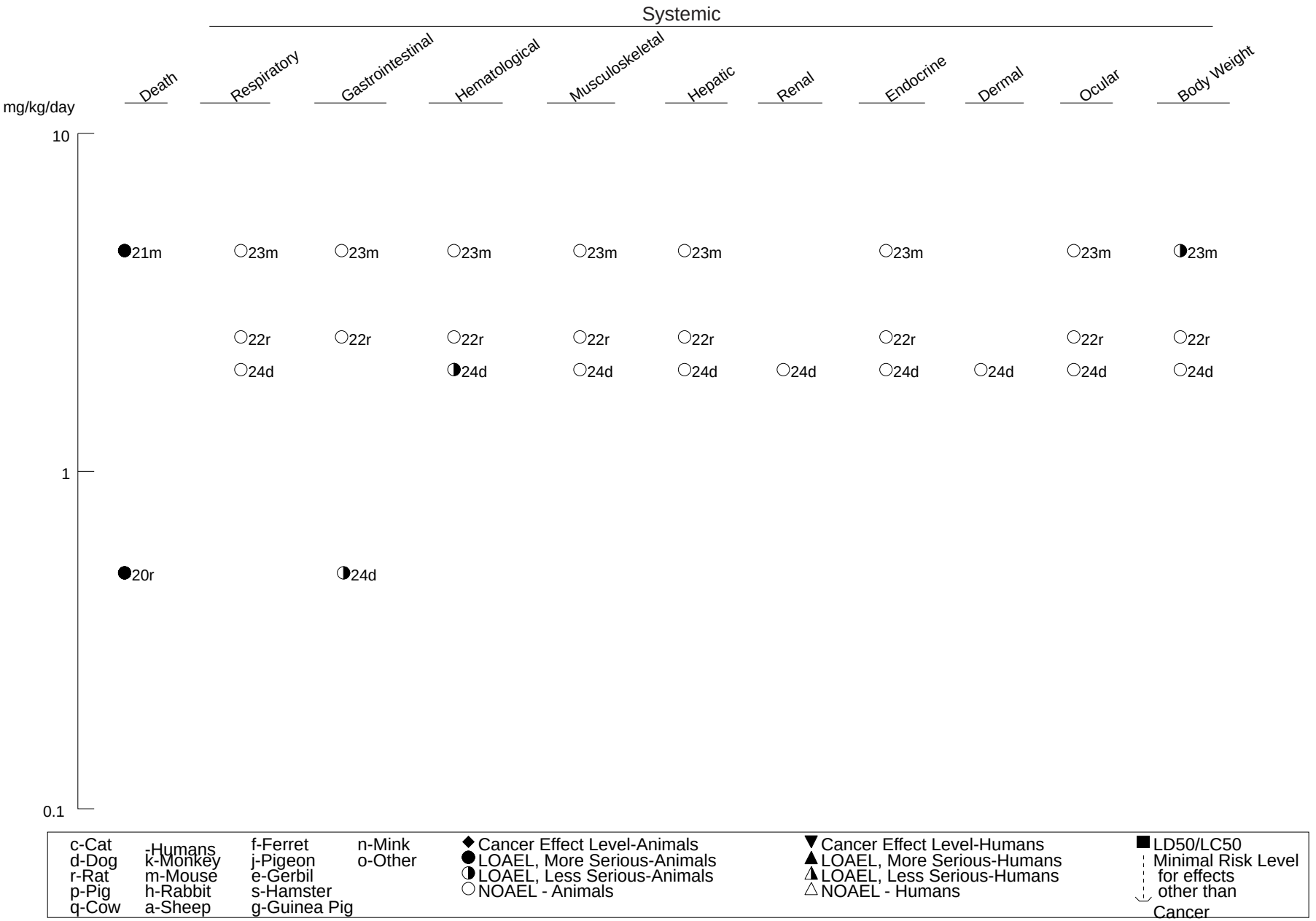


Figure 3-2 Levels of Significant Exposure to Acrolein - Oral

Chronic (≥365 days)



Cardiovascular Effects. Histopathological examination of the cardiovascular system revealed no effects after intermediate-duration exposure to acrolein in rats (King 1984) or after chronic exposure in rats (Parent et al. 1992a), mice (Parent et al. 1991), or dogs (Parent et al. 1992b).

Gastrointestinal Effects. Gastrointestinal irritation is the primary effect of oral exposure to acrolein. Though the clinical signs are consistent and dose-related across acute and intermediate exposures, possible adaptation to irritating effects may have important implications for chronic exposures. Rats administered a single gavage dose of 25 mg/kg of acrolein in saline showed severe multifocal ulceration of the forestomach and glandular stomach 48 hours after dosing, though no controls were used for comparison. The areas of ulceration showed severe inflammation, focal hemorrhage, and edema (Sakata et al. 1989). Gastric mucosa ulcerations were also observed in rabbits given gavage doses of 4 mg/kg/day during gestational days 7–19 (Parent et al. 1993) and in rats given gavage doses of 5.4 mg/kg/day for 115 days (King 1984). Stomach necrosis and hemorrhage were observed in female rats gavaged with 5 mg/kg/day, male mice and rats gavaged with 10 mg/kg/day, and female mice gavaged with 20 mg/kg/day for 13 weeks (NTP 1995). Forestomach squamous epithelial hyperplasia was observed in male and female rats gavaged with 2.5 and 1.25 mg/kg/day, respectively, for 13 weeks (NTP 1995), while glandular stomach squamous epithelial hyperplasia was seen in male and female mice gavaged with 1.25 and 2.5 mg/kg/day, respectively, for the same time period. Glandular stomach hyperplasia, ulcers, and hemorrhage were found in rats gavaged with 3 mg/kg/day for 93–149 days (Parent et al. 1992c). No significant gastrointestinal effects of acrolein exposure, however, were reported in rats (Parent et al. 1992a), mice (Parent et al. 1991), or dogs (Parent et al. 1992b) after chronic gavage dosing with up to 2.5, 4.5, or 2 mg/kg/day, respectively. While no unusual gross pathological lesions in the gastrointestinal tract were observed in dogs given up to 2 mg/kg/day for 12 months (Parent et al. 1992b), increased incidences of vomiting were observed shortly after dosing, suggesting gastrointestinal irritation. However, adaptation seemed to occur in the 2 mg/kg/day group as late as 51 weeks into the study, as vomiting frequency was sharply reduced compared to the first 4 weeks of the study. Based on the occurrence of forestomach squamous epithelial hyperplasia in rats given gavage doses of acrolein, an intermediate-duration MRL of 0.008 mg/kg/day has been calculated from the NOAEL of 0.75 mg/kg/day (NTP 1995). Although humans do not have a forestomach, this study provides an example of gastrointestinal mucus membrane irritation. Similar irritative effects are expected in humans.

Hematological Effects. No significant hematological effects were observed in rats given gavage doses of up to 7.2 mg/kg/day acrolein for 115 days (King 1984), in mice given gavage doses of up to

4.5 mg/kg/day acrolein for 18 months (Parent et al. 1991), or in rats given gavage doses of up to 2.5 mg/kg/day for 2 years (Parent et al. 1992a). In dogs, decreased prothrombin times were seen in females while decreased serum protein, albumin, and calcium levels were observed in both sexes given 2 mg/kg/day for 12 months (Parent et al. 1992b). In the same study, mean corpuscular hemoglobin concentration (MCH) and mean corpuscular volume (MCV) were significantly increased in male dogs, but were depressed in females given gavage doses of 0.5 or 2 mg/kg/day. The authors could not provide an explanation for these hematological changes, but state that the changes were not thought to be toxicologically meaningful.

Musculoskeletal Effects. No histopathological changes were observed in musculoskeletal tissues of rats after intermediate-duration exposure (King 1984). Similarly negative results were obtained in rats (Parent et al. 1992a), mice (Parent et al. 1991), and dogs (Parent et al. 1992b) chronically exposed to acrolein, although the specific muscular tissues observed were not reported.

Hepatic Effects. Altered liver or kidney weights were reported in rats administered 1.5 mg/kg/day acrolein in drinking water for 30 days (Smyth et al. 1951), although no liver or kidney weight changes occurred following administration of 0.17 mg/kg/day. It is unclear if the altered organ weight occurred in the liver and/or kidneys, or if the organ weights increased or decreased. Decreased relative liver weights occurred in male mice gavaged with 10 mg/kg/day for 13 weeks (NTP 1995). No liver effects were observed upon gross pathological or histological examinations in rats after intermediate-duration exposure to 7.2 mg/kg/day acrolein (King 1984). Similarly, no significant hepatic changes were found in rats (Parent et al. 1992a), mice (Parent et al. 1991), or dogs (Parent et al. 1992b) after chronic exposure to 2.5, 4.5, or 2 mg/kg/day acrolein, respectively. Reduced serum protein, albumin, and calcium levels were observed in dogs chronically given 2 mg/kg/day (Parent et al. 1992b). It is uncertain as to whether these effects are indicative of hepatic changes, as the authors of this study reported that there were no dose-related differences in liver pathology.

Renal Effects. As mentioned previously, altered kidney or liver weights were reported by Smyth et al. (1951) in rats given 1.5 mg/kg/day acrolein in drinking water for 30 days, with no effect on liver or kidney weights resulting from administration of 0.17 mg/kg/day. It is unclear from the report whether there was an alteration in kidney weight or liver weight or both, or if the organ weights increased or decreased. Reddish-brown urine was observed in rats during intermediate-duration exposure to 6 mg/kg/day (Parent et al. 1992c). No histopathological changes were reported in kidneys of rats after intermediate-duration exposure to 7.2 mg/kg/day (King 1984) or in rats (Parent et al. 1992b), mice (Parent

et al. 1991), and dogs (Parent et al. 1992a) after chronic exposure to 2.5, 4.5, or 2 mg/kg/day acrolein, respectively. Negative results were also obtained from the urinalysis of dogs exposed to 0.05–2 mg/kg/day for 12 months (Parent et al. 1992b).

Dermal Effects. No studies were located regarding dermal effects in humans following oral exposure to acrolein.

No dermal effects were observed in rats receiving an intermediate-duration exposure of 7.2 mg/kg/day (King 1984).

Ocular Effects. No treatment-related ocular effects were reported in rats (Parent et al. 1992a), mice (Parent et al. 1991), or dogs (Parent et al. 1992b) chronically exposed to acrolein.

Body Weight Effects. Rats treated with 6 mg/kg/day and rabbits treated with 2 mg/kg/day during gestation days 7–10 exhibited reduced body weight gains (King 1982; Parent et al. 1993), but the rabbits resumed body weights comparable to controls thereafter. Decreased body weight gains were reported in rats given intermediate-duration exposures of 6 and 7.2 mg/kg/day (King 1984; Parent et al. 1992c) and in mice given 4.5 mg/kg/day for 18 months (Parent et al. 1991). No significant body weight changes were observed in dogs given 2 mg/kg/day for 12 months (Parent et al. 1992b) or in rats given 2.5 mg/kg/day for 2 years (Parent et al. 1992a).

Other Systemic Effects. Statistically significant decreases in total serum protein, albumin, and calcium were observed in dogs given 2 mg/kg/day acrolein for 12 months (Parent et al. 1992b). Serum creatinine phosphokinase levels were depressed in rats given 0.05–2.5 mg/kg/day for 24 months (Parent et al. 1992a). However, the toxicological significance of these findings is not clear, since no treatment-related effects were observed in any organs or tissues upon gross pathological or histological examination.

3.2.2.3 Immunological and Lymphoreticular Effects

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

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to acrolein.

Slow response to stimuli, body sag, loss of elevation reflexes, and poor body tone were observed in rats exposed to a single oral dose of 11.2 mg/kg acrolein (Sprince et al. 1979). The usefulness of this study in assessing the neurotoxic effects of oral exposure to acrolein is limited. It is difficult to determine whether these observed effects are direct toxicological effects attributed to acrolein treatment or nonspecific responses of animals at the point of death.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to acrolein.

Exposure of rats to 10 mg/kg/day acrolein during pregnancy had no effect on the number of implantations or resorptions or on the ratio of live/dead fetuses per litter (King 1982). No evidence of acrolein reproductive toxicity was found in a two-generation study in which rats of each generation were exposed to 7.2 mg/kg/day for 100–120 days prior to mating and then for 15 days during mating (King 1984). Reproductive performance was not affected in two generations of male and female rats given 1, 3, or 6 mg/kg/day acrolein for 96–149 days (Parent et al. 1992c). Offspring of rabbits given 0.1–2 mg/kg/day on gestation days 7–19 were not observed to have premature deliveries, spontaneous abortions, or statistically significant gross or soft tissue malformations or variations (Parent et al. 1993). However, in the preliminary dose-range study reported by Parent et al. (1993), a dose-related, but statistically untested, increase in embryonic resorptions was observed after exposure of dams to 1 mg/kg/day or more. No explanation for this discrepancy was given in the study, although the treatment groups in the range-finding study had only 3–4 animals, while the groups in the full study had 20 animals. No fetuses were alive in the litters of dams that were administered 4 mg/kg/day acrolein. The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

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

Developmental effects have been observed in animals after oral exposure. In a preliminary dose-range finding study, exposure of rabbits to ≥1 mg/kg/day resulted in dose-related increased incidences of fetal resorption (Parent et al. 1993); however, fetal mortality was not affected in the primary study, in which rabbits were exposed to ≤2 mg/kg/day during gestation. No explanation for the discrepancy was provided, though maternal body weight loss in the range-finding study may have confounded fetal effects. It should be noted that the range-finding study utilized only 3–4 animals/dose group, while the definitive study used 20 animals/group, suggesting that greater weight should be given to the data from the full study. Body weights of pups from rats given 6 mg/kg/day through gestation and lactation were significantly reduced during gestation. Otherwise, litter viability and size, gestation duration, and pup growth and morphology were unaffected by acrolein exposure of the dams (Parent et al. 1992c). Increased incidences of skeletal anomalies and delayed ossification and decreased mean fetal weight and total litter weights were observed in the offspring of rats exposed to 10 mg/kg/day (King 1982). This dosage, however, was toxic to the dams, resulting in maternal deaths. The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located regarding carcinogenic effects in humans after oral exposure to acrolein.

Limited evidence of the carcinogenicity of acrolein in animals is provided by a few long-term studies. Lijinsky and Reuber (1987) reported a cancer bioassay in which groups of male rats were given acrolein in the drinking water at concentrations that provided doses of 0, 6, 14, or 36 mg/kg/day, 5 days/week for 104–124 weeks. One group of females was also given the highest dose on the same schedule as the males. The only indication of a carcinogenic effect of acrolein was the incidence of neoplasms of the adrenal cortex in high-dose female rats. The increased incidence of hyperplastic nodules of the adrenal cortex in 2 of 20 female rats was significant with respect to controls. Other studies failed to detect significant cancer incidence in animals. Gavage treatment of rats with 0.05–2 mg/kg/day failed to produce tumor incidences, including adrenal tumors, which were significantly different from controls (Parent et al. 1992a). Extensive histopathological examination did not reveal any carcinogenic effects in mice (Parent et al. 1991), or dogs (Parent et al. 1992b) after oral exposure to 2.5, 4.5, or 2 mg/kg/day acrolein, respectively, for 12–24 months. Because of the disparate results of the Lijinsky and Reuber (1987) and Parent et al. (1991 and 1992a) studies, an independent pathology working group (PWG) re-

evaluated the Lijinsky and Reuber tumor data (cited in Parent et al. 1992c). The PWG concluded that the incidence of cortical tumors in treated females was within the limits of historical controls and were of no biological significance for adrenal cancer from acrolein exposure.

The DHHS has not classified acrolein as to its carcinogenicity (NTP 2005). IARC has determined that acrolein is not classifiable as to carcinogenicity in humans (IARC 2004). The EPA has stated that the potential carcinogenicity of acrolein cannot be determined based on an inadequate database (IRIS 2005).

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding lethality in humans after dermal exposure to acrolein.

In rabbits administered several dilutions of acrolein percutaneously, the LD_{50} values ranged from 160 to 1,000 mg/kg body weight, depending on the vehicle and concentration (Albin 1962). Salaman and Roe (1956) painted the backs of mice with 5 ppm acrolein (in sesame oil) for 10 weeks for a total dose of 12.6 mg and reported that acrolein did not cause mortality.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects in humans or animals after dermal exposure to acrolein. Reliable LOAELs for systemic effects in humans are presented in Table 3-3.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after dermal exposure to acrolein. When applied topically to the eyes of rabbits, acrolein (dose not reported) increased the heart rate (Basu et al. 1971). However, this effect is most likely due to the painful stimulation of the eye.

Dermal Effects. A 57-year-old man who accidentally spilled acrolein over his genital area experienced swelling of the penis and scrotum. After 15 days, the genital area was deeply ulcerated and gangrenous. No follow-up information was provided (Schöning 1966). Volunteers receiving topical applications of a 10% solution of acrolein in ethanol exhibited irritation, papillary edema,

Table 3-3 Levels of Significant Exposure to Acrolein - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
ACUTE EXPOSURE							
Systemic							
Human	1 d	Dermal			10 Percent (%) (severe skin irritation)	Lacroix et al. 1976	
Human	1 d 5-10 min	Ocular		0.81 ppm (eye irritation)	1.22 ppm (eye irritation)	Sim & Pattle 1957	
Human	1 d 7.5min/d	Ocular		0.3 B ppm (eye irritation)		Weber-Tschopp et al. 1977	

d = day; LOAEL = lowest-observed-adverse-effect level; min = minute(s); NOAEL = no-observed-adverse-effect level

polymorphonuclear infiltrates, and epidermal necrosis 48 hours after exposure (Lacroix et al. 1976). Accidental exposure to vapors of acrolein produced burns of the cheeks and eyelids in a male subject (Champeix et al. 1966).

Ocular Effects. Volunteers reported statistically significant eye irritation in two of three different vapor-exposure scenarios (Weber-Tschopp et al. 1977). In 90-second fixed-concentration exposures, 0.6 ppm resulted in a significant increase in the number of positive reports scoring irritation as "a little." In an exposure to gradually increasing acrolein levels in which participants were queried every 5 minutes as to irritation, a significant number of positive reports of irritation, scored as "a little", were generated at the end of the first interval when the concentration was measured to be 0.09 ppm. Lastly, eye irritation from a 60-minute, 0.3-ppm exposure was scored by participants as "a little" at 10 minutes and "medium" at 40 minutes with no further increase in severity. In another human study, lacrimation occurred within 20 seconds in individuals exposed to 0.81 ppm, and within 5 seconds at 1.22 ppm (Sim and Pattle 1957). Human data summarized by Kane and Alarie (1977) show concentrations of acrolein between 0.5 and 5 ppm caused lacrimation and various degrees of eye irritation in exposure periods of 10 minutes or less.

The ocular effects observed in experimental animals are qualitatively similar to those described in humans. Concentrations of acrolein higher than 1.0 ppm (1.8–3.7 ppm) caused eye irritation in dogs and monkeys as evidenced by lacrimation and closing of the eyes, but guinea pigs and rats appeared to be less sensitive, since 3.7 ppm had no noticeable effect (Lyon et al. 1970). No histological evaluation of the eye was conducted, but other reports indicate that ocular discharge was commonly seen (Murphy et al. 1964; Skog 1950).

3.2.3.3 Immunological and Lymphoreticular Effects

Rappaport and Hoffman (1941) reported the case of a male smoker who developed a severe skin reaction on the fingers of his right hand (which he used to hold the cigarette) and on his upper and lower lips. The patient was subjected to numerous allergy tests and found to be sensitive to acrolein, as well as other simple, short-chain aldehydes. It should be noted that this individual, a histology laboratory worker, was also likely to be exposed frequently to formaldehyde. It is difficult to determine whether the immunological response was a result of exposure to acrolein or other aldehydes.

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

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

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

No studies were located regarding carcinogenic effects in humans after dermal exposure to acrolein.

Salaman and Roe (1956) applied acrolein (in sesame oil) to the backs of mice once a day for 10 weeks. The total dose applied was 12.6 mg (5% solution). The authors reported no tumors at the site of application or at remote sites. These results should be interpreted with caution, since the duration of the study was too short to evaluate carcinogenic potential, and only 15 mice were used.

3.3 GENOTOXICITY

No studies were located regarding the genotoxic effects of acrolein in humans or animals by inhalation, oral, or dermal routes. Acrolein was not mutagenic *in vivo* as judged by the dominant lethal assay in the mouse (Epstein et al. 1972) or the sex-linked recessive lethal test in *Drosophila* (Zimmering et al. 1985).

The *in vitro* genotoxicity of acrolein has been investigated in prokaryotic and eukaryotic organisms and in mammalian cell systems. The overall evidence, presented in Table 3-4, indicates that acrolein is weakly mutagenic without activating systems and non-mutagenic in the presence of activating systems in *Salmonella typhimurium* and *Escherichia coli*. In the yeast, *Saccharomyces cerevisiae*, acrolein was not mutagenic without activating systems. In mammalian cells, acrolein gave positive results without activating systems. Acrolein inhibited the activity of DNA polymerase as well as DNA and RNA synthesis in rat liver cell nuclei.

Acrolein also induced chromosome breakage and sister-chromatid exchange in Chinese hamster ovary cells. DNA damage was seen in human myeloid cells and bronchial cells in culture. Acrolein was not mutagenic to normal human fibroblasts in culture, but fibroblasts with a deficient DNA repair system

Table 3-4. Genotoxicity of Acrolein *In Vitro*

End point	Species (test system)	Results[a] With activation	Results[a] Without activation	Reference
Prokaryotic organisms:				
Gene mutation	*Salmonella tymphimurium* plate incorporation	–	–	Andersen et al. 1972
		–	–	Florin et al. 1980
		–	–	Loquet et al. 1981
		–	–	Bignami et al. 1977
		–	(+)	Lijinsky and Andrews 1980
		–	+	Lutz et al. 1982
		–	+	Eder et al. 1982
		–	–	Basu and Marnett 1984
		No data		Bartsch et al. 1980
		No data	(+)	Khudoley et al. 1987
	Liquid preincubation test	No data	+	Marnett et al. 1985
	Liquid preincubation method	No data	+	Foiles et al. 1989
		–	(+)	Waegemaekers and Bensink 1984
	Escherichia coli PQ37 (SOS chromotest)	–	–	Von der Hude et al. 1988
	E. coli K-12/343/113 (plate incorporation)	–	No data	Ellenberger and Mohn 1977
	WPuvrA (plate incorporation)	No data	(+)	Hemminki et al. 1980
	DNA polymerase deficiency (plate incorporation)	No data	+	Bilimoria 1975
	E. coli AB1157 derivatives	–	No data	VanderVeen et al. 2001
Eukaryotic organisms:				
Fungi:				
Gene mutation	*Saccharomyces cerevisiae* (plate incorporation)	No data	–	Izard 1973
Chromosomal aberrations	*S. cerevisiae* MB1072-2B (plate incorporation)	No data	–	Fleer and Brendel 1982
Mammalian cells:				
DNA, RNA synthesis	Rat liver cell nuclei	No data	+	Moule et al. 1971
DNA synthesis	Human fibroblasts (xeroderma pigmentusum and HeLa cells)	No data	–	Yang et al. 2002a
DNA polymerase activity	Rat liver	No data	+	Munsch et al. 1973, 1974
Chromosome breakage	Chinese hamster ovary cells	+	+	Au et al. 1980

Table 3-4. Genotoxicity of Acrolein *In Vitro*

End point	Species (test system)	Results[a] With activation	Results[a] Without activation	Reference
Sister chromatid exchange	Chinese hamster ovary cells	+	+	Au et al. 1980
DNA damage	Human myeloid cells K562	No data	+	Crook et al. 1986a
DNA damage	Human bronchial cells (culture)	No data	+	Grafstrom et al. 1988
DNA repair	Human bronchial cells (culture)	No data	+	Krokan et al. 1985
DNA repair	Human fibroblasts (culture)	No data	–	Curren et al. 1988
DNA repair	Human fibroblasts (xeroderma pigmentation)	No data	+	Curren et al. 1988
Gene mutation	Chinese hamster V79 cells	No data	+	Smith et al. 1990a
Gene mutation	Human fibroblasts (with *supF* plasmids)	No data	+	Kawanishi et al. 1998
Gene mutation	Human fibroblasts (xeroderma pigmentusum and HeLa cells)	No data	–	Yang et al. 2002a

+ = positive result; – = negative result; (+) = marginally positive result; DNA = deoxyribonucleic acid; RNA = ribonucleic acid

showed a positive mutagenic response (Curren et al. 1988). Acrolein was also a potent inhibitor of the DNA repair enzyme 0_6-methylguanine-DNA methyl transferase. DNA base substitutions and intra-strand cross-links were observed in human fibroblasts containing shuttle vector plasmids bearing the *supF* marker gene (Kawanishi et al. 1998). The mechanism by which acrolein induces genotoxicity in mammalian cells is not known, but it has been shown that acrolein can form adducts with DNA, such as $1N_2$-propanodeoxyguanine (Chung et al. 1984; Foiles et al. 1989) and $1N_6$-propanodeoxyadenine (Smith et al. 1990a). Yang et al. (2002b) showed that acrolein adduction to DNA may be insignificant for the introduction of miscoding errors, as translesion DNA synthesis was high and miscoding incidence was <1% in human HeLa and xeroderma pigmentosum cells. The same inability of acrolein DNA adducts to cause miscoding was observed in *E. coli* as well (VanderVeen et al. 2001). Because of the limited number of *in vivo* tests, there is insufficient evidence to predict that acrolein poses a genotoxic threat to humans.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were located regarding the rate and extent of absorption in humans after inhalation exposure to acrolein. The collection of such data would be problematic, as acrolein is highly reactive with any nucleophilic binding site it encounters during exposure by any route.

Egle (1972) exposed anesthetized dogs to concentrations of acrolein between 172 and 262 ppm for a brief period of time (1–3 minutes) and observed that acrolein uptake by the total respiratory tract at ventilation rates of 6–20 respirations/minute averaged 80–85% of the inhaled dose. Retention was independent of the respiratory rate. The author estimated that only about 20% of the inhaled dose reached the lower respiratory tract. Morris et al. (1996, 2003) exposed mice to 1.1 ppm and rats to 0.9–9.1 ppm acrolein. In both species, most of the inhaled acrolein was absorbed entirely into the upper respiratory tract. Mice absorbed 92% of 1.1 ppm over 10 minutes. Absorption in the upper respiratory tract of rats was found to be dose- and breathing-rate related. At a breathing rate of 50 mL/minute, absorption ranged from >90% to approximately 70% for 0.9–9.1 ppm, while approximately 50–30% was absorbed when breathing 300 mL/minute of the same concentrations for 40 minutes.

Exposure of the lower respiratory tract alone resulted in 65–70% concentration-independent retention, but decreased slightly with increases in tidal volume from 100 to 160 mL. Although the study by Egle (1972) does not provide information on the disposition of the retained acrolein or on whether the uptake rates represent steady-state values, it indicates that acrolein at relatively high concentrations is effectively removed from inhaled air by both the upper and lower respiratory tracts.

3.4.1.2 Oral Exposure

No studies were located regarding absorption in humans after oral exposure to acrolein.

Very little information is known about the absorption of acrolein following oral exposure. Based on toxicological effects observed after oral administration of acrolein, it is assumed to be absorbed through the gastrointestinal tract. However, the rate and extent of absorption are not known.

3.4.1.3 Dermal Exposure

No studies were located regarding absorption in humans after dermal exposure to acrolein. In cases of accidental dermal exposure (described in Section 3.2.3), effects were restricted to the exposed region of the body, presumably because of the high reactivity of acrolein.

Limited information is available regarding dermal absorption of acrolein in animals. The percutaneous LD_{50} for rabbits ranged from 160 to 1,000 mg/kg, depending on the acrolein concentration and vehicle (water or mineral spirits) (Albin 1962). LD_{50}values for acrolein administered in mineral spirits are lower than those in which water served as the vehicle, likely because of the greater skin permeability of mineral spirits.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals after inhalation exposure to acrolein.

3.4.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to acrolein.

In a study conducted by Draminski et al. (1983), the acrolein conjugated metabolite S-carboxyethyl-mercapturic acid was identified in the urine of rats after oral administration of a single dose of 10 mg/kg of acrolein. This study provides indirect evidence of distribution of acrolein to the liver and kidney, where conjugation most likely occurred.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to acrolein.

3.4.3 Metabolism

There is limited information available regarding the metabolism of acrolein in humans and animals after inhalation, oral, and dermal exposures. The relevant data are presented below.

In non-biological cell-free systems, acrolein forms thiol ethers within seconds when reacted with glutathione or cysteine (Esterbauer et al. 1975, 1976). In cell systems *in vitro*, such as cultured human bronchial cells and isolated cell preparations from rat liver and kidneys, acrolein forms conjugates with glutathione, cysteine, N-acetylcysteine, and/or thioredoxin (Dawson et al. 1984; Dupbukt et al. 1987; Gurtoo et al. 1981b; Yang et al. 2004; Zitting and Heinonen 1980). The formation of these conjugates greatly diminished the cytotoxic effects of acrolein, indicating that conjugation may be an important detoxification mechanism. In addition to the evidence provided by the numerous *in vitro* studies, two reports from the literature demonstrated that acrolein also reacts with glutathione *in vivo*. In these studies, the acrolein metabolite 3-hydroxypropylmercapturic acid was identified in the urine of rats after a subcutaneous dose of acrolein (Alarcon 1976; Kaye 1973). It should be noted that other compounds also metabolize to 3-hydroxypropylmercapturic acid, including allylamine (Boor et al. 1987), allyl halides (Kaye et al. 1972), and allyl alcohol and ester (Kaye 1973).

Based on experimental results, Patel et al. (1980b) proposed an *in vitro* metabolic scheme for acrolein in rat liver and lung preparations. In this scheme, free acrolein can interact with proteins and nucleic acids,

and/or with thiol groups such as glutathione. Acrolein can also be transformed into acrylic acid by liver cytosol or microsomes, or it can be oxidized to glycidaldehyde by lung or liver microsomes. Acrylic acid may be incorporated into amino acids, fatty acids, and sterol. Glycidaldehyde can be metabolized to glyceraldehyde, which then can enter the glycolytic pathways. From the scheme proposed by Patel et al. (1980b), glycidaldehyde appears to be the only chemical that could represent a risk to human health, since it has shown carcinogenic properties in mice and rats when applied dermally (Shamberger 1974; Van Duuren 1967a, 1967b). The metabolic pathway proposed by Patel et al. (1980b) is shown in Figure 3-3.

3.4.3.1 Inhalation Exposure

No studies were located regarding metabolism in humans after inhalation exposure to acrolein.

Lam et al. (1985) found a dose-related depletion of glutathione in the nasal respiratory mucosa of rats after exposure to 0.1–2.5 ppm of acrolein for 3 hours. This finding is consistent with a chemical reaction leading to the formation of a glutathione-acrolein adduct.

3.4.3.2 Oral Exposure

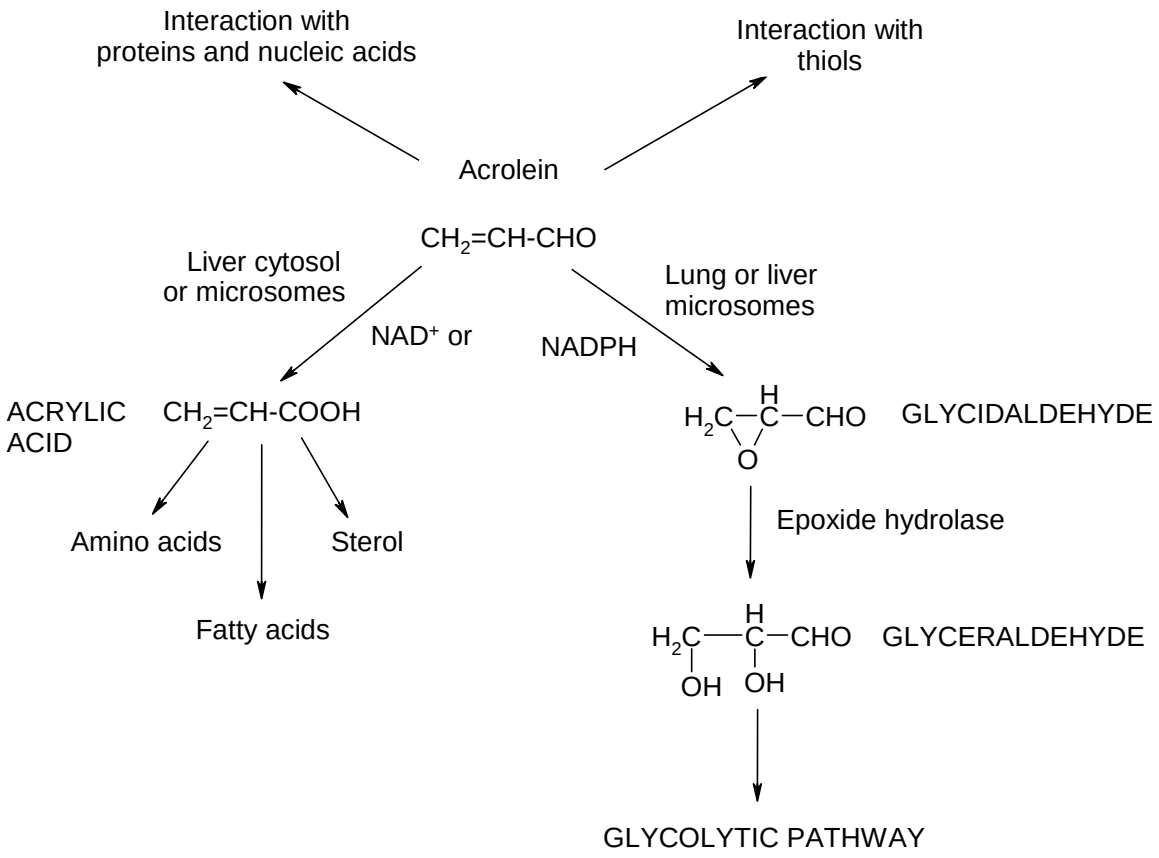
No studies were located regarding metabolism in humans after oral exposure to acrolein.

Draminski et al. (1983) administered 10 mg/kg of acrolein as a single oral dose to rats and collected the urine during 3 days. Since the metabolite S-carboxyethylmercapturic acid was found in the urine, but S-hydroxypropylmercapturic acid (which should have been formed if acrolein had reacted with glutathione) was not, an alternative pathway was proposed. In this metabolic scheme, acrolein is first metabolized to acrylic acid with subsequent formation of the methyl ester, which is then conjugated with glutathione to form S-carboxyethylmercapturic acid methyl ester. Both metabolic schemes proposed by Draminski et al. (1983) and Patel et al. (1980b) involve the hepatic formation of acrylic acid, but differ on the subsequent metabolism of that metabolite. The metabolic pathway postulated by Draminski et al. (1983) is shown in Figure 3-4.

3.4.3.3 Dermal Exposure

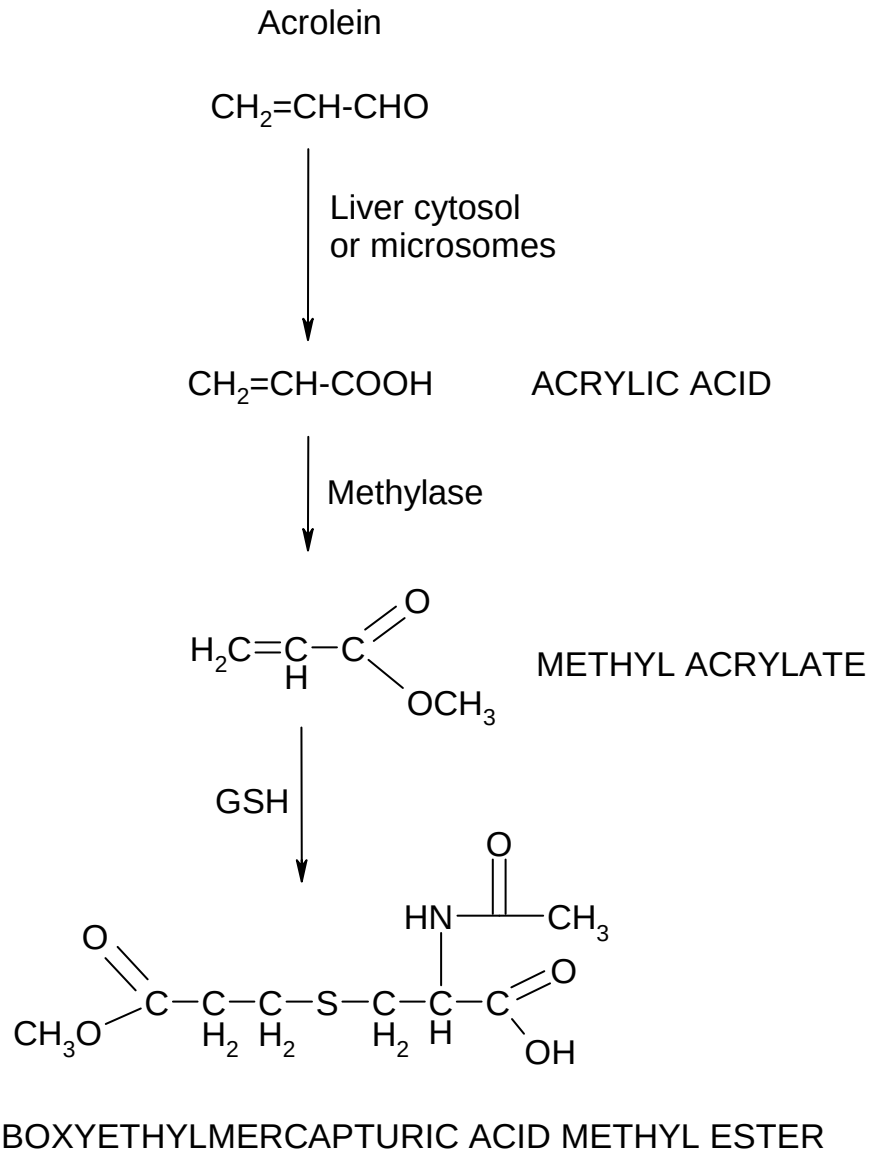
No studies were located regarding metabolism in humans or animals after dermal exposure to acrolein.

Figure 3-3. Proposed Metabolic Scheme for Acrolein *In Vitro*



Source: Patel et al. 1980

Figure 3-4. Proposed Metabolic Scheme for Acrolein *In Vivo*



Source: Draminski et al. 1983

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No studies were located regarding excretion in humans or animals after inhalation exposure to acrolein.

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to acrolein.

Draminski et al. (1983) reported the presence of the acrolein metabolite S-carboxyethylmercapturic acid in the urine of rats after administration of a single oral dose of 10 mg/kg of acrolein. The percentage of the dose recovered as the metabolite in the urine was not determined.

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to acrolein.

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.

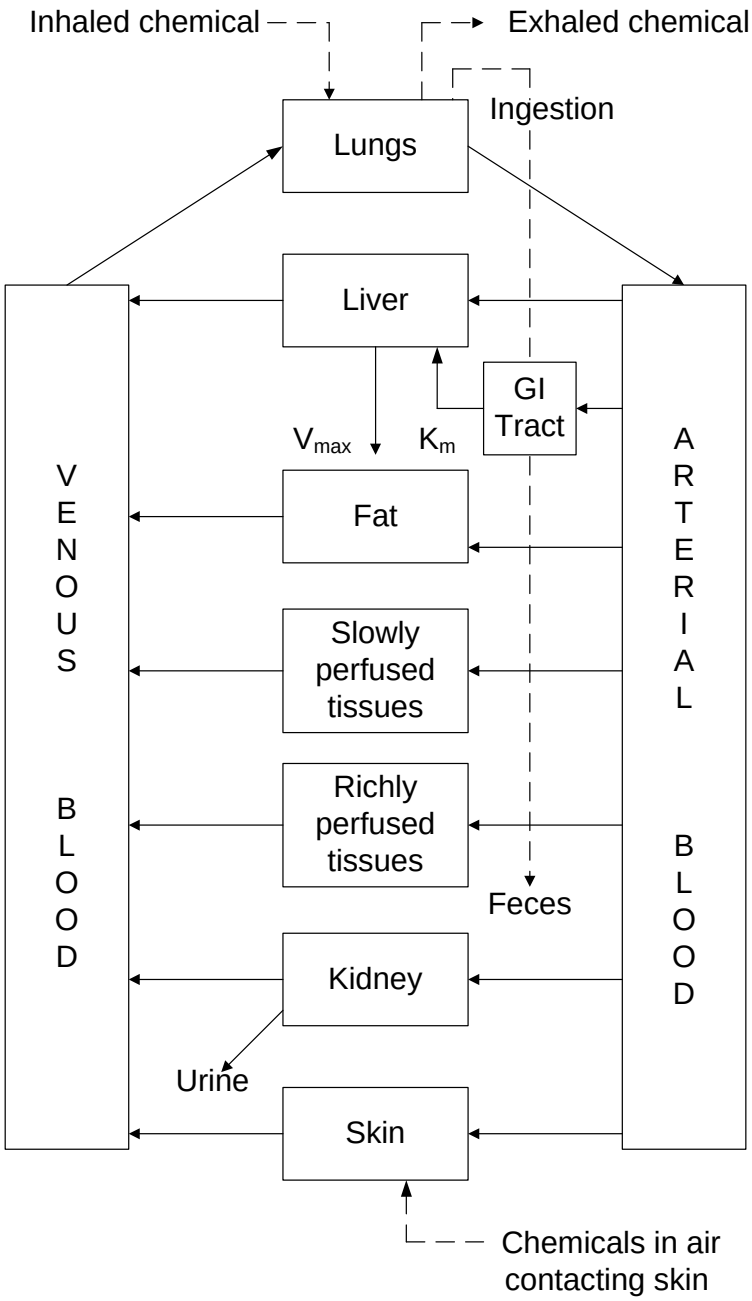
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically 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. If the uptake and disposition of the chemical substance(s) are adequately described, however, 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 3-5 shows a conceptualized representation of a PBPK model.

No PBPK models for acrolein were identified in the literature.

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

No studies were located for animals or humans that describe observed mechanisms for acrolein absorption across the skin, lung, or gut, metabolism (either through passive adduct formation or enzymatically catalyzed transformation), or excretion. It is not known whether acrolein and its metabolites are transported across cell membranes via passive diffusion or active transport processes. Since acrolein is known to react with any nucleophilic site, including protein thiol moieties, peptide-based active transporters may form adducts with acrolein, which may serve to diminish or inhibit the transporter's functionality.

3.5.2 Mechanisms of Toxicity

As an ethenylic aldehyde, acrolein is a highly reactive compound. In biological systems, it binds extensively to lysine moieties and has the highest affinity for sulfhydryl groups found on many cellular molecules, including most proteins. As such, it binds rapidly and irreversibly to macromolecules to form thiol ethers (Beauchamp 1985). In this fashion, acrolein may bind to structural and biological messenger compounds to produce direct cytotoxic effects or secondary effects from interrupted cell signaling pathways. Alarie et al. (1973) hypothesized that rapid binding of acrolein to neural receptors in the corneal and nasal mucosa may result in rapid depolarization of the associated neurons to produce ocular and nasal irritation. Adams and Klaidman (1993) showed acrolein to bind rapidly to glutathione. Depletion of glutathione could be inhibitory to the enzyme glutathione peroxidase, resulting in a lower level of cellular protection against oxygen radical toxicity. Further, the adduction of glutathione resulted in generation of a GS-propionaldehyde, which was shown to produce oxygen and possibly hydroxy radicals via cytosolic aldehyde dehydrogenase. Arumugan et al. (1999) exposed rats to 1 and 2 ppm acrolein for 4 hours and measured various markers for lipid peroxidation in lavage fluid from the lung. They found diminished glutathione levels in treated animals as well as an increase in superoxide dismutase and decreases in catalase and glutathione peroxidase, indicative of an imbalance in antioxidant defenses that favors oxidative stress. Further, increased levels of conjugated dienes and thiobarbituric acid reactive substances suggest the onset of lipid peroxidation. They were further able to correlate changes in peroxidative status on the lungs with gross histological findings of desquamated alveolar endothelium, a metaplastic change in cell structure that has been observed over the entire respiratory tract

of animals. Beauchamp's analysis (1985) suggests that depletion of glutathione and other available cellular thiol sources may permit the movement of acrolein at high concentrations past the initial tissue point of contact. While data were not found that correlated gastrointestinal lesions with glutathione content and peroxidative status as was done in the lung (Arumugan et al. 1999), the appearance of endothelial metaplasia in multiple species of animals following oral exposures suggests that gastrointestinal and respiratory toxicity may occur by the same mechanism of action.

Acrolein has been shown to be produced endogenously from hydroxyl-amino acids (Anderson et al. 1997) and as a product of lipid peroxidation (Uchida et al. 1998a, 1998b), which can form protein conjugates that may be significant factors in certain diseases. Acrolein conjugation with lysine residues of low-density lipoproteins has been suggested as a factor in the development of atheroclerosis (Uchida 1998b). Protein-acrolein binding products resulting from lipid peroxidation have been implicated in the formation of neurofibrillary tangles (Calingasan et al. 1999) and induction of protein tau hyperphosphorylation (Gomez-Ramos et al. 2003), both hallmarks of Alzheimer's disease.

3.5.3 Animal-to-Human Extrapolations

The irritant properties of acrolein have been reported in both human and animal studies. *In vivo* studies in animals and *in vitro* studies in human and animal cell cultures have reported the common mechanisms of action of cellular thiol reactivity and glutathione depletion (Arumugan et al. 1999; Beauchamp 1985; Nardini et al. 2002). Acrolein exposure levels were very comparable for the appearance of cellular changes in nasal epithelium of animals (Cassee et al. 1996) and onset of nasal irritation in humans (Weber-Tschopp et al. 1977). Therefore, it is reasonable to extrapolate animal health effects to human health risk resulting from acrolein exposure.

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 Colborn and Clement (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 acrolein. No *in vitro* studies were located regarding endocrine disruption of acrolein. Based on the mechanism of toxicity and data from animal studies (Parent et al. 1991, 1992a, 1992b), acrolein is not expected to have endocrine-modulating activities.

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 all 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 hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to 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, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage 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). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). 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 who all have a low glomerular filtration rate and have not 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).

Since point-of-contact irritation is the principal toxic action of acrolein, children are not likely to be more susceptible to acrolein's effects at the tissue level. Despite uncertainties in age-related differences in lung architecture, surface area, and ventilation rates, simple dosimetry modeling of a category 1 gas, such as acrolein, does not suggest significant differences in early juvenile and adult internal inhalation exposure (Ginsberg et al. 2005). It is not known if there are age-related differences in the pharmacokinetics of acrolein. The amount of ingested acrolein available for gastrointestinal irritation would be the same for children and adults. While children may have a higher inhalation rate (per mass) than adults (NRC 1993), it is unknown whether they would continue to breathe more airborne acrolein than adults. While adults have been shown to reduce their respiration rate by as much as 20% in the presence of airborne acrolein (Weber-Tschopp et al. 1977), it is not known if children will react in the same or similar manner. Animal studies have shown offspring of acrolein-exposed mothers to have reduced body weights and skeletal deformities (King 1982; Parent et al. 1992c). However, these effects occurred at high oral doses that were fatal to the mothers.

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).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. 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 acrolein 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 acrolein 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 Acrolein

A product of the conjugation of acrolein with glutathione, 3-hydroxypropylmercapturic acid, has been identified in the urine of individuals receiving the drug cyclophosphamide (Alarcon 1976; Kaye and Young 1974). Since the same product was identified in the urine of rats administered acrolein subcutaneously (Alarcon 1976), it was thought that levels of 3-hydroxypropylmercapturic acid in the urine could be used to identify exposure to acrolein. However, Alarcon (1976) found no correlation between the dose of cyclophosphamide administered and the amount of 3-hydroxypropylmercapturic acid in the urine of patients. Methods developed to determine levels of acrolein in human tissues and fluids are described in Chapter 7.

3.8.2 Biomarkers Used to Characterize Effects Caused by Acrolein

No studies were located regarding levels of acrolein or its metabolites in human tissues and fluids associated with effects. No biochemical or histological changes specific for acrolein exposure were identified. Results from a toxicokinetic study suggested that acrolein can react with proteins and nucleic acids in the organism (Patel et al. 1980b).

After transformation into acrylic acid, incorporation into amino acids, fatty acids, and sterols can be expected (Patel et al. 1980b). However, specific effects associated with these biochemical reactions are not known.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Ansari et al. (1988a) showed that acrolein enhances the inhibitory effect that certain industrial chemicals, such as styrene and 1,2-dichloroethane, have on the αl-proteinase inhibitor of human plasma *in vitro*. A decrease in the activity of the αl-proteinase inhibitor may result in an increase in the activity of the lung enzyme neutrophil elastase, which can lead to the development of emphysema. Acrolein has also been shown to increase the pentobarbital- and hexobarbital-induced sleeping time in rats (Jaeger and Murphy 1973a). The mechanism, according to the authors, could include changes in the absorption and distribution of the barbiturates. More recent information suggests that the mechanism may involve a covalent reaction between acrolein and cytochrome P-450 leading to inactivation of P-450 resulting in prolonged action of the barbiturates (Lame and Segall 1987).

Acrolein forms adducts with thiols such as glutathione, cysteine, N-acetylcysteine, and others. Such reaction protects tissues and cells from the cytotoxic effects of acrolein or acrolein-releasing substances (Brock et al. 1981b; Chaviano et al. 1985; Dawson et al. 1984; Gurtoo et al. 1983; Ohno and Ormstad 1985; Whitehouse and Beck 1975).

Exposure of mice for 10 minutes to mixtures of sulfur dioxide and acrolein showed that either irritant can alter or block the effect of the other (Kane and Alarie 1979a). Furthermore, when the mice were exposed to mixtures, recovery was much slower than when exposed to the individual chemicals. The authors postulated that a bisulfite-acrolein adduct may be formed. When exposure ceased, this adduct would release acrolein, thus preventing immediate recovery. In addition, Kane and Alarie (1978) exposed mice to mixtures of acrolein and formaldehyde and showed that the respiratory response to mixtures was less

pronounced than the response to either chemical alone. This is consistent with a mechanism in which both chemicals act on the same type of physiological receptor (free nerve endings).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to acrolein than will most persons exposed to the same level of acrolein in the environment. Reasons 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 acrolein, or compromised function of organs affected by acrolein. Populations who are at greater risk due to their unusually high exposure to acrolein are discussed in Section 6.7, Populations with Potentially High Exposures.

In general, individuals whose respiratory function is compromised, such as those with emphysema, or individuals with allergic conditions such as asthma, will be at a higher risk of developing adverse respiratory responses when exposed to a strong respiratory irritant such as acrolein. This was demonstrated in animals in which allergic airway-diseased mice were more responsive than nondiseased mice to acute respiratory irritant effects of 0.3 ppm acrolein (Morris et al. 2003).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

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

Bronstein AC, Currance PL. 1994. Emergency care for hazardous materials exposure. 2nd ed. St. Louis, MO: Mosby Lifeline.

ITII. 1988. Toxic and hazardous industrial chemicals safety manual. Tokyo, Japan: The International Technical Information Institute.

Sullivan JB, Krieger GR, eds. 1992. Hazardous materials toxicology-clinical principles of environmental health. Baltimore, MD: Williams and Wilkins.

3.11.1 Reducing Peak Absorption Following Exposure

The absorption of acrolein following inhalation or oral exposures is not known. Since acrolein is a point-of-contact irritant, measures to dilute the concentration at the pulmonary, gastrointestinal, or dermal tissue surfaces may reduce absorption. Emergency treatment for acrolein inhalation exposure includes ventilation and oxygenation. Water may be ingested or used as a rinse to dilute oral or dermal exposures, respectively. Gastric lavage or nasogastric suction may be administered if life-threatening amounts of acrolein are ingested (HSDB 2005).

3.11.2 Reducing Body Burden

Acrolein is not believed to accumulate in the body. With the exception of gastric lavage and nasogastric suction (see Section 3.11.1), no studies or guidelines could be located with procedures for reducing the body burden of acrolein.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Acrolein acts by contact reactivity (i.e., adduction) with nucleophilic sites on macromolecules of biological tissues, including binding to glutathione. There are no clinically-accepted procedures for therapeutically interfering with acrolein's toxic mechanism of action. Several *in vitro* and *in vivo* studies suggest candidates for treatment of acrolein exposure at the cellular level. The anti-hypertensive drug hydrazinophthalazine is effective in trapping reactive acrolein-protein adducts formed following *in vitro* acrolein exposure of mouse hepatocytes (Burcham et al. 2004) and *in vivo* intraperitoneal allyl alcohol (which is metabolized to acrolein) exposure in mice (Kaminskas et al. 2004). Effective *in vitro* and *in vivo* concentrations of hydrazinophthalazine ranged from 2 to 50 µM and from 6 to 18 mg/kg, respectively. Pretreatment of rat A10 aortic smooth muscle cells with 1,2-dithiole-3-thione resulted in induction of cellular glutathione and glutathione-S-transferease (an enzyme that catalyzes the conjugation of reduced glutathione and reactive electrophiles, such as acrolein) and a marked decrease in acrolein cytotoxicity (Cao et al. 2003). Cells treated with 100 µM 1,2-dithiole-3-thione were 90–100% viable after 24 hours of exposure to as much as 40 µM acrolein. The antioxidants α-tocopherol and ascorbic acid served to significantly reduce acrolein-induced apoptosis (25 µM) in cultured human bronchial epithelial cells at levels of 5 and 50 µM, respectively (Nardini et al. 2002). While these studies report a variety of compounds and cellular concentrations capable of interfering with acrolein's toxic mechanism

of action, they do not provide data regarding an effective administered dose (by any route) or maximum delay in administration that would provide efficacy against acrolein toxicity in humans or animals.

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

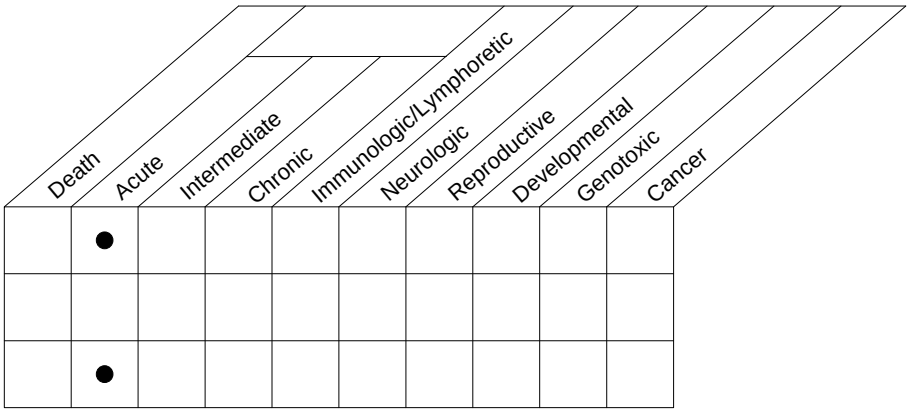
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean 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.

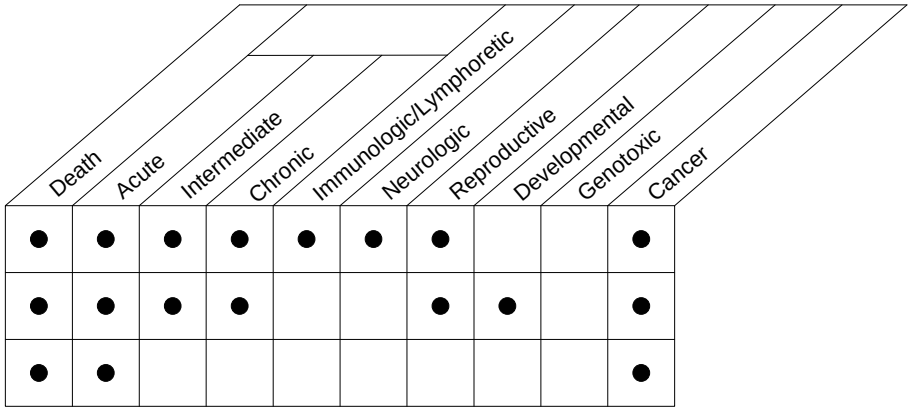
3.12.1 Existing Information on Health Effects of Acrolein

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to acrolein are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of acrolein. 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.

As seen from Figure 3-6, very little information is available regarding the health effects of exposure of humans to acrolein. Experimental studies in humans have attempted to determine the thresholds for eye,

Figure 3-6. Existing Information on Health Effects of Acrolein





Inhalation

nose, and throat irritation. Information on humans accidentally exposed to acrolein also indicates that acrolein irritates the skin, eyes, nose, and throat, and that severe respiratory effects can persist long after exposure occurs.

Data are available for acute and intermediate inhalation exposures that resulted in death of animals. For the most part, these exposures also affected the respiratory tract and the immune response to bacterial agents.

An intermediate inhalation exposure study of rats prior to mating and during pregnancy did not result in fetotoxic or teratogenic effects. Limited information is available regarding chronic inhalation exposure.

Data are available for oral doses associated with death and increased mortality in acute, intermediate, and chronic exposure. The developmental and reproductive effects of oral exposure to acrolein have also been investigated. Chronic oral exposure of female rats may have resulted in neoplasms in the adrenal cortex, though the data are equivocal.

Acrolein applied to the skin of animals results in skin irritation and death if applied in high concentration. Acrolein was not carcinogenic when applied to the skin of mice for 10 weeks.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Acute inhalation exposure to acrolein is irritating to the upper respiratory system in humans (Sim and Pattle 1957; Weber-Tschopp et al. 1977) and animals (Cassee et al. 1996). The respiratory tract is the primary target of acrolein toxicity via inhalation exposure. Desquamation of the respiratory epithelium followed by airway occlusion and asphyxiation was the main reason for acrolein-induced mortality in animals (Ballantyne et al. 1989; Catilina et al. 1966; Crane et al. 1986; Skog 1950). An MRL for acute inhalation exposure was derived from human data (Weber-Tschopp et al. 1977) for respiratory effects. No data were located regarding acrolein toxicity in humans after oral exposure. Information regarding acute oral exposure of animals is limited to developmental toxicity studies (King 1982; Parent et al. 1993). The lowest LOAEL between the two studies, 2 mg/kg/day in rabbits, resulted in significant decrement in weight gain followed by a rebound to control values. This transient effect on body weight was not observed in non-pregnant animals. It is not known if pregnancy contributed to the reversal of effect on body weight. Therefore, the acute oral data are not sufficient to derive an MRL. Acute-duration oral exposure studies in non-pregnant animals need to be

performed using low doses about which clinical effects have been observed (i.e., vomiting in dogs from 0.5 mg/kg [Parent et al. 1992b]). Histological examination of the gastrointestinal tissues may provide data regarding sensitive irritant effects, such as epithelial metaplasia, that may serve as a basis for an acute MRL.

Skin contact with acrolein caused irritation, burns, and epidermal necrosis in humans (Champeix et al. 1966; Lacroix et al. 1976; Schöning 1966). It is evident, therefore, that the necrotic effects of acrolein occur at the site of primary contact regardless of routes of exposure. Target organs for acrolein toxicity other than at the site of contact, however, were not identified and pharmacokinetic data are insufficient to identify target organs across routes of exposure. Further studies describing the tissue-specific pharmacokinetics of acrolein after exposure via all three routes would be useful. The information is important for populations living near hazardous waste sites that might be exposed to acrolein for brief periods of time.

Intermediate-Duration Exposure. No studies were located regarding intermediate-duration exposure to acrolein in humans. Inhalation exposure studies in animals (Costa et al. 1986; Feron et al. 1978; Kutzman et al. 1984; Lyon et al. 1970) suggest that the respiratory tract is the most sensitive target of toxicity for inhaled acrolein. The information was sufficient for derivation of an inhalation MRL (Feron et al. 1978). Oral exposure studies in animals (King 1984; NTP 1995; Parent et al. 1992b) provide strong evidence that the stomach is the most sensitive target of toxicity. An intermediate-duration oral MRL was based on histological changes in the gastrointestinal tract of rats (NTP 1995). Studies are needed to assess the dermal effects of intermediate-duration exposures. While intermediate-duration data are available for ocular irritation in animals (Lyon et al. 1970), no data are available for the effects of acrolein exposure to skin. Studies examining effects on the skin of intermediate-duration exposures to acrolein would be of limited utility, as acrolein in the environment evaporates rapidly from water and binds significantly to nucleophilic sites in soil-born matter, likely resulting in low bioavailability.

Chronic-Duration Exposure and Cancer. No studies were located regarding toxicity in humans following chronic exposure. Respiratory toxicity was observed in rats and hamsters after inhalation exposure (Feron and Kruysse 1977; Le Bouffant et al. 1980). However, the designs of these inhalation studies were not sufficient for MRL derivation. The studies used short daily exposures that are not indicative of chronic exposure, or had only one exposure level, which would not provide a NOAEL and corresponding LOAEL. Chronic-duration inhalation studies with multiple exposure levels and having extensive daily exposure periods are needed to derive a chronic-duration inhalation MRL. Chronic oral

studies were performed in rats, mice, and dogs (Parent 1992b; Parent et al. 1991, 1992a). Extensive histopathological examination revealed no effects in any organs. Reduced survival of mice and rats (a frank effect level) was observed, although no cause of death could be determined. Chronic-duration oral studies identifying a NOAEL and/or less serious LOAEL are needed to derive a chronic-duration oral MRL. No studies were located regarding acrolein toxicity after chronic-duration dermal exposure in animals. Studies describing the effects of acrolein associated with chronic, low-level exposure of the skin would be useful.

No studies were located regarding the carcinogenicity of acrolein in humans. No increase in tumor incidence was observed in two limited, chronic inhalation studies in animals. These studies either had a very short daily exposure of 1 hour (Le Bouffant et al. 1980) or were carried out for less-than-lifetime duration for the study animals (Feron and Kruysse 1977; Le Bouffant et al. 1980). Dermal application of acrolein to mice for ten weeks did not induce cancer (Salaman and Roe 1956). However, the length of the study is considered too short for proper evaluation of carcinogenicity. No carcinogenic effect was found in rats, mice, and dogs following extensive histopathological examinations after chronic oral exposure to acrolein (Parent 1992b; Parent et al. 1991, 1992a). An increased incidence of adrenocortical adenomas was observed in female rats after oral exposure to acrolein in another study (Lijinsky and Reuber 1987); however, these findings were challenged by an independent pathology working group. In order to better assess the carcinogenicity of acrolein, a chronic, lifetime-duration animal study needs to be performed to include a dose approaching the maximum tolerated chronic dose.

Genotoxicity. No studies were located regarding acrolein genotoxicity in humans. Dominant lethality of acrolein was not observed in mice (Epstein et al. 1972). However, *in vitro* data showed weak mutagenic potential of acrolein in bacterial and mammalian cells without metabolic activation (Table 3-4). Further studies in animals would be useful to determine the ability of acrolein to induce chromosomal aberrations after exposure. Cytogenetic analysis of peripheral lymphocytes of workers exposed to acrolein would provide an opportunity to assess its genotoxicity in humans.

Reproductive Toxicity. No studies were located regarding reproductive effects of acrolein in humans. No changes in reproductive organs of rats after intermediate and chronic oral exposures or in mice or dogs after chronic exposures were found during histopathological examination (Parent 1992b; Parent et al. 1991, 1992a). No reproductive effects were observed in rats after inhalation exposure to acrolein (Bouley et al. 1975). The results of a multi-generation oral exposure study in rats were also negative (King 1984). Although not reproduced in the main study, the statistically-untested results of a

pilot dose-range study indicated increased fetal resorptions in rabbits after oral exposure to acrolein (Parent et al. 1993). Furthermore, dominant lethality was induced in mice exposed to acrolein by inhalation. These data indicated possible reproductive effects of acrolein exposure in animals, and further studies would be useful to support these results. No data were located regarding reproductive effects in animals after dermal exposure, and the pharmacokinetic data are insufficient to draw any conclusion. Further studies of reproductive toxicity following dermal exposure in animals would be useful for extrapolating the results to human exposure.

Developmental Toxicity. No studies were located regarding developmental effects of acrolein in humans by any route of exposure. Increased incidences of skeletal anomalies and delayed ossification were observed in orally-exposed rats (King 1982). Furthermore, the results from parenteral administration indicate that acrolein may cross the placenta, causing malformations and embryolethality in experimental animals (King 1982). This information is particularly relevant to individuals who are receiving the drug cyclophosphamide, of which acrolein is a metabolite. The developmental effects after inhalation or dermal exposure in animals were not studied. Pharmacokinetic data are insufficient to predict developmental effects after these routes of exposure. Further animal studies providing information on pre- and postnatal developmental toxicity of acrolein after oral, inhalation, and dermal exposure would be useful. The information is important for possible extrapolation of results to human exposure.

Immunotoxicity. Information regarding immunological effects of acrolein in humans is limited to a single case study (Rappaport and Hoffman 1941). No information regarding immunological effects in animals after oral or dermal exposure to acrolein was located. Acute and subchronic inhalation studies indicate that acrolein may increase the risk of bacterial infections in the respiratory tract (Aranyi et al. 1986; Bouley et al. 1975; Sherwood et al. 1986). Studies using a battery of immunotoxicity tests to correlate exposure intensity with specific end points of immune response would provide a more sensitive assessment of possible immunotoxic effects than histological examination of tissues and organs of the immune system. Since a possible case of an allergic response to acrolein derived from cigarette smoke was described in humans (Rappaport and Hoffman 1941), sensitization tests could help identify agents causing allergic responses in individuals exposed to tobacco smoke.

Neurotoxicity. No information was located regarding neurological effects of acrolein in humans. Symptoms of central nervous system depression were observed in rodents after oral exposure to acrolein, but only after lethal concentrations (Sprince et al. 1979). No such effects were observed in animals after

inhalation exposure; the animals died from asphyxia caused by epithelial desquamation and, consequently, respiratory obstruction (Ballantyne et al. 1989; Catilina et al. 1966; Crane et al. 1986; Skog 1950). No behavioral changes were observed in animals exposed to acrolein by any route. Nonspecific histopathological effects on the brains of animals were found in subchronic inhalation studies (Feron et al. 1978; Kutzman et al. 1984, 1985; Lyon et al. 1970). No histopathological changes in neurological tissues were observed after oral exposure (Parent et al. 1991, 1992a, 1992b). No studies regarding neurotoxicity of acrolein after dermal exposure were located. However, the available data do not indicate that the central nervous system is the major target of acrolein toxicity. No data needs have been identified at this time.

Epidemiological and Human Dosimetry Studies. The only information available concerning effects of acrolein in humans comes from two acute inhalation studies involving volunteers (Sim and Pattle 1957; Weber-Schopp et al. 1977) and a limited number of cases of accidental inhalation (Bauer et al. 1977; Champeix et al. 1966; Gosselin et al. 1979) and dermal (Schöning 1966) exposures to unknown levels of acrolein (Champeix et al. 1966; Gosselin et al. 1979; Lacroix et al. 1976; Schöning 1966). In these cases, extremes in severity, either quickly reversible eye and respiratory irritation or severe burns of the eyes and respiratory tract mucosa (with some effects persisting for several months), were observed. No epidemiological studies are available. Epidemiology studies correlating the severity of end points such as respiratory and gastrointestinal epithelial metaplasia (obtained by histology of the pulmonary and gastric mucosa) with exposure intensity and duration are needed. Such studies would be useful for identifying effects of long term exposure to tolerable concentrations. This information would be useful for establishing the existence of a dose-response relationship for chronic human exposures and for monitoring individuals near hazardous waste sites for preventive purposes.

Biomarkers of Exposure and Effect.

Exposure. No reliable biomarkers of acrolein exposure have been identified. The finding of 3-hydroxypropylmercapturic acid in the urine after exposure to acrolein or cyclophosphamide seemed to be promising for use as an exposure identifier (Kaye and Young 1974). However, further studies found no correlation between the amount of 3-hydroxypropylmercapturic acid in the urine and the dose of parent compound administered (Alarcon 1976). Further identification of acrolein metabolites in the urine and their correlation with levels of exposure would be useful. Iype et al. (1987) presented preliminary results in an abstract regarding the development of an antibody-mediated assay to monitor subjects exposed to acrolein; however, these data are not available in a full, peer-reviewed publication. This assay exploits

the possible formation of acrolein-adducted DNA in cells, or the formation of antibodies against such adducts in serum. Assays for acrolein-adducted DNA, thiols, and lysine could possibly be used to aid in etiology of respiratory diseases such as bronchitis, to which acrolein may be a contributor. Further studies regarding possible biochemical changes after acrolein exposure would be useful.

Effect. As with biomarkers for exposure, no studies were located for animals or humans that correlated the concentration of acrolein or its metabolites with toxic effects in target tissues. No biochemical or histological changes specific to acrolein exposure have been identified in humans or animals. Although transformation, and subsequent incorporation into macromolecules, of acrolein to acrylic acid has been identified (Patel et al. 1980b), no specific health effects of these reactions are known. Studies designed to correlate the appearance of adduction products and metabolites with increasingly severe acrolein-induced lesions may be useful in identifying "fingerprints" of metabolites to serve as biomarkers of effect.

Absorption, Distribution, Metabolism, and Excretion. There are no data available sufficient to derive the rates of acrolein absorption, distribution, metabolism, or excretion. Toxicokinetic data of acrolein are from the *in vivo* absorption study in dogs (Egle 1972) and rats (Morris 1996) and the oral exposure study in rats by Draminski et al. (1983), from which a possible metabolic pathway was proposed. However, dermal and inhalation exposures may very different absorption rates and lead to different metabolic pathways and patterns of distribution and excretion, which could account for differences in the degree of toxicity exhibited by different routes of exposure. The metabolism of acrolein *in vitro* seems to be well understood, including the reaction with glutathione (Patel et al. 1980b). This reaction represents an important mechanism for the protection of cells and tissues from the cytotoxic effects of acrolein. Determining the urinary excretion of acrolein conjugates in control volunteers and in individuals known to have been exposed to polluted environments could provide information concerning absorption and excretion of the xenobiotic. The use of human cell lines in culture might be considered a useful alternative to studying the metabolic fate of acrolein.

Comparative Toxicokinetics. No studies were located regarding comparative toxicokinetics of acrolein *in vivo*. Differences in the toxicokinetics of a chemical among species may account for differences in toxic responses. Though similar inhalation effects have been observed in rats and humans (Cassee et al. 1996; Weber-Tschopp et al. 1977) at comparable exposure levels, the animal species that serves as the best model for extrapolating results to humans remains unknown. Although virtually no information is available regarding the toxicokinetics of acrolein in humans, analysis of the urine of

individuals occupationally exposed to the chemical would provide valuable information on absorption and excretion rates, provided that exposure to acrolein could be reasonably estimated.

Methods for Reducing Toxic Effects. Acrolein is known to react rapidly with nucleophilic groups in every type of tissue (Beauchamp 1985). While systemic metabolism of acrolein to toxic metabolites has been proposed, animal studies (Morris 1996; Morris et al. 2003) and human case reports (Champeix et al. 1966; Gosselin et al. 1979) suggest that point-of-contact toxicity dominates the onset of adverse health effects. For this reason, simple dilution of acrolein at the point of tissue contact may provide the best protection against acrolein-induced injury and obviate the need for data concerning the reduction of toxic effects. Indeed, the standard treatments for inhalation, oral, and dermal acrolein exposures are provision of fresh air, ingestion of water, and copious rinsing with water, respectively (HSDB 2005). No data needs have been identified at this time.

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

Although no data are available describing age-related differences in acrolein toxicity, acrolein is expected to affect children by the same mechanisms through which it affects adults. However, data are needed to determine if tissue-specific, age-related differences exist for glutathione levels, possibly resulting in an increased sensitivity to acrolein, particularly for respiratory effects. Children with asthma and reactive airway dysfunction may exhibit effects at levels different than adults with similar sensitivities.

3.12.3 Ongoing Studies

A. Bhatnagar, University of Louisville, Louisville, Kentucky, is identifying and defining the cardiovascular effects (an example of subtle, low-dose effects) of environmental aldehydes and pollutants that generate aldehydes (FEDRIP 2005). The project will integrate molecular and cellular aspects of aldehyde toxicity, delineate the contribution of individual pathways involved in the detoxification of the aldehydes, and elucidate how aldehydes affect atherosclerosis, platelet and endothelial activation, and myocardial function. Acrolein and trans-2-hexanal will be studied as model aldehydes most prevalent in the environment.

4. CHEMICAL AND PHYSICAL INFORMATION

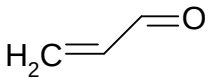
4.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of acrolein are listed in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of acrolein are presented in Table 4-2.

Table 4-1. Chemical Identity of Acrolein

Characteristic	Information	Reference
Synonyms	Acraldehyde, acrylic aldehyde, acrylaldehyde, allyl aldehyde, ethylene aldehyde, 2-propenal, propylene aldehyde	HSDB 2005; RTECS 2004
Trade name	Aqualin, Biocide, Crolean, MAGNACIDE B®, MAGNACIDE H®, Slimicide	RTECS 2004
Chemical formula	C_3H_4O	HSDB 2005
Chemical structure		
Identification numbers:		
CAS registry	107-02-8	HSDB 2005
NIOSH RTECS	AS1050000	RTECS 2004
EPA hazardous waste	P003	HSDB 2005
OHM/TADS	7216793	OHM/TADS 1988
DOT/UN/NA/IMCO shipping	UN 1092	HSDB 2005
IMCO	3.1	HSDB 2005
HSDB	177	HSDB 2005
NCI	Not available	

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

Table 4-2. Physical and Chemical Properties of Acrolein

Property	Information	Reference
Molecular weight	56.06	O'Neil 2001
Color	Colorless or yellowish	Lewis 1997
Physical state	Liquid	Lewis 1997
Melting point	-87.7 °C	Lide 2000
Boiling point	52.6 °C	Lide 2000
Density at 20 °C	0.840 g/cm^3	Lide 2000
Odor	Disagreeable, choking odor, pungent	Lewis 1997; O'Neil 2001
Odor threshold:		
Water	0.11 ppm	Amoore and Hautala 1983
Air	0.16 ppm	Amoore and Hautala 1983
Solubility:		
Water at 25 °C	2.12x10^5 mg/L	Seidell 1941
Organic solvents	Miscible with lower alcohols, ketones, benzene, diethyl ether, and other common organic solvents	Tomlin 2003
Partition coefficients:		
Log K_{ow}	-0.01	Hansch and Leo 1995
Log K_{oc}	51–270	Irwin 1988
Vapor pressure at 25 °C	274 mmHg	Daubert and Danner 1987
Henry's law constant at 25 °C	1.22x10^{-4} atm-m^3/mol	Gaffney et al. 1987
Autoignition temperature	220 °C	HSDB 2005
Flashpoint	-18 °C (open cup) -26 °C (closed cup)	HSDB 2005; O'Neil 2001
Flammability limits	2.8–31 volume %	HSDB 2005
Conversion factors		
Air	1 ppm (v/v)=2.328 mg/m^3 1 mg/m^3=0.43 ppm (v/v)	Verschueren 2001

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

5.1 PRODUCTION

Acrolein was first produced commercially in the 1930s through the vapor phase condensation of acetaldehyde and formaldehyde (Etzkorn et al. 2002). A second method was developed in the 1940s, which involved the vapor phase oxidation of propylene; however, this method was not used at first due to the poor performance of cuprous oxide catalysts. During the 1960s, propylene oxidation was greatly enhanced by the introduction of bismuth molybdate-based catalysts and has since become the primary method used for the commercial production of acrolein. Acrylic acid and carbon oxides are the major byproducts produced during this reaction. Minor byproducts are acetaldehyde, acetic acid, formaldehyde, and polyacrolein.

Companies located in the United States that currently produce acrolein are: Baker Petrolite Corporation, Taft, California; Degussa Corporation, Theodore, Alabama; and Dow Chemical U.S.A., Taft, Louisiana (SRI 2004). Annual production capacities reported during the year 2000 were 110,000 metric tons/year (242 million pounds/year) for the Degussa Corporation and 72,000 metric tons/year (159 million pounds/year) for Dow Chemical (Etzkorn et al. 2002). Production capacity data were not provided for the Baker Petrolite Corporation. In 1978, domestic manufacturing plants produced approximately 354 million pounds of acrolein (Anderson 1983). The production volumes of acrolein reported by manufacturers in 1986, 1990, 1994, 1998, and 2002 were within the ranges of >10–50 million pounds, >50–100 million pounds, >50–100 million pounds, >100–500 million pounds, and >100–500 million pounds, respectively (IUR 2002).

Table 5-1 summarizes information on companies that reported the production, import, or use of acrolein for the Toxics Release Inventory in 2002 (TRI02 2005). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

5.2 IMPORT/EXPORT

Current information regarding the import or export of this compound could not be located.

Table 5-1. Facilities that Produce, Process, or Use Acrolein

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	5	0	999,999	1, 3, 5, 6, 13
AR	1	0	99	1, 5
CA	3	0	999,999	1, 5, 9, 12
GA	3	0	9,999	1, 5
IA	1	0	99	1, 5
IL	2	0	999	1, 5
IN	1	10,000	99,999	6
KS	1	100	999	1, 13
LA	14	0	10,000,000,000	1, 3, 4, 5, 6, 7, 8, 12, 13
ME	1	0	99	1, 5
MI	2	0	9,999	1, 5, 12
MN	2	0	99,999	1, 5
MS	1	0	99	1, 5
NC	2	0	9,999	1, 5
NE	1	1,000	9,999	1, 13
NY	1	1,000,000	9,999,999	12
OH	1	1,000	9,999	1, 13
OR	1	0	99	1, 5, 13
SD	1	0	99	1, 5
TN	1	100,000	999,999	8, 9
TX	41	0	9,999,999	1, 3, 4, 5, 6, 7, 9, 10, 12, 13
VA	1	0	99	1, 5
WI	1	0	99	1, 5
WV	1	0	99	1, 5

Source: TRI02 2005 (Data are from 2002)

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

5.3 USE

The largest single use for acrolein is as an unisolated intermediate in the manufacture of acrylic acid, most of which is converted to its lower alkyl esters (IARC 1995). Acrolein is also used as a herbicide and algicide in irrigation waters and drainage ditches; as a biocide in the control of algae, weeds, and mollusks in recirculating process water systems; as a slimicide in the paper industry; as a biocide in oil wells and liquid petrochemical fuels; in the cross-linking of protein collagen in leather tanning; as a tissue fixative in histological samples; in the manufacture of colloidal forms of metals; in the production of perfumes; as a warning agent in methyl chloride refrigerant; and as an intermediate in the manufacture of methionine and its hydroxyl analogue, glutaraldehyde, ally1 alcohol, pyridines, and tetrahydrobenz-aldehyde (Arntz et al. 2002; Baker Petrolite 2005; Etzkorn et al. 2002; Hess et al. 1978; HSDB 2005; IARC 1995; Lewis 1997; O'Neil 2001; Windholz 1983). Isolated, refined acrolein is used mainly as a biocide and as an intermediate in the production of methionine, which is a protein supplement used in animal feed (Arntz et al. 2002; IARC 1995). Acrolein has been used to make modified food starch, synthetic glycerine, acrolein polymers, polyeurethane, and polyester resins (Arntz et al. 2002; HSDB 2005; Lewis 1997). It has also been used in military poison gas mixtures (IARC 1995).

5.4 DISPOSAL

Prior to implementing land disposal of waste residues (including waste sludge), environmental regulatory agencies should be consulted for guidance on acceptable disposal practices (HSDB 2005). Materials containing concentrated acrolein may be incinerated by: rotary kiln incineration, with a temperature range of 820–1,600 °C and a residence time of seconds; fluidized bed incineration, with a temperature range of 450–980 °C and a residence time of seconds; and liquid injection, with a temperature range of 650–1,600 °C and a residence time of 0.1–2 seconds (HSDB 2005). Materials containing small amounts of acrolein may be disposed of by neutralization (if needed), followed by secondary biological treatment or by submerged combustion (to concentrate the waste) followed by incineration (Hess et al. 1978; OHM-TADS 1988). On-site combustion is an option for disposal if the spill site is in a very remote, inaccessible area, and there is danger of subsequent discharge if other methods of disposal are attempted. Local, state, and federal Resource Conservation and Recovery Act (RCRA) approval must be obtained before burning on site (OHM-TADS 1988).

Acrolein has been identified as a hazardous waste by the EPA, and the disposal of this compound is regulated under RCRA. Specific information regarding federal regulations concerning disposal of hazardous wastes through land treatment, landfilling, incineration, thermal treatment, chemical/physical/biological treatment, underground injection, and deep sea injection are provided in the Code of Federal Regulations (40 CFR 190–399). Release of acrolein in waste water is regulated under the Clean Water Act by the National Pollutant Discharge Elimination System (NPDES).

Information regarding effluent guidelines and standards for acrolein may be found in 40 CFR 122, 40 CFR 125, 40 CFR 268, 40 CFR 413, 40 CFR 423, and 40 CFR 433.

Pursuant to RCRA Section 3004(g)(5), EPA has proposed to restrict the land disposal of acrolein (EPA 1989b). Acrolein may be land disposed only if prior treatment standards have been met, or if disposal occurs in units that satisfy the statutory no migration standard (EPA 1989b). Proper guidelines and standards are outlined in the Federal Register (EPA 1989b).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

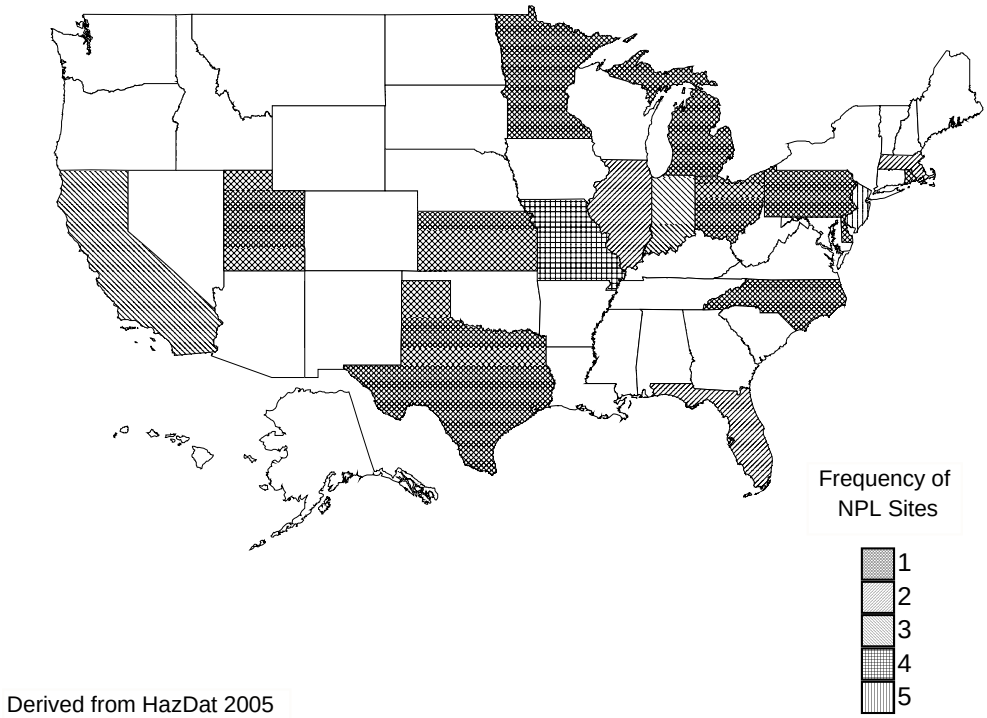
Acrolein has been identified in at least 31 of the 1,662 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2005). However, the number of sites evaluated for acrolein is not known. The frequency of these sites can be seen in Figure 6-1.

Acrolein may be released to the environment in emissions and effluents from its manufacturing and use facilities, in emissions from combustion processes (including cigarette smoking and combustion of petrochemical fuels), from direct application to water and waste water as a slimicide and aquatic herbicide, as a photooxidation product of various hydrocarbon pollutants found in air (including propylene and 1,3-butadiene), and from land disposal of some organic waste materials. Acrolein is a reactive compound and is unstable in the environment.

In ambient air, the primary removal mechanism for acrolein is predicted to be reaction with photochemically generated hydroxyl radicals (half-life, 15–20 hours). Products of this reaction include carbon monoxide, formaldehyde, and glycolaldehyde. In the presence of nitrogen oxides, peroxynitrate and nitric acid are also formed. Small amounts of acrolein may also be removed from the atmosphere in precipitation. Insufficient data are available to predict the fate of acrolein in indoor air. In water, small amounts of acrolein may be removed by volatilization (half-life, 23 hours from a model river 1 m deep), aerobic biodegradation, or reversible hydration to β-hydroxypropionaldehyde, which subsequently biodegrades. Based on the reactivity of acrolein, it is expected that removal of acrolein from water through the binding of the chemical to dissolved and suspended organics will become increasingly important as the concentration of the organics in water increases. However, information on this removal process could not be located.

Half-lives of <1–3 days for small amounts of acrolein in surface water have been observed. When highly concentrated amounts of acrolein are released or spilled into water, this compound may polymerize by oxidation or hydration processes. In soil, acrolein is expected to be subject to removal through volatilization, abiotic and biotic degradation processes, and possibly irreversible binding to soil components. This compound can be highly mobile in soil; however, this movement is expected to be attenuated by the removal processes given above.

Figure 6-1. Frequency of NPL Sites with Acrolein Contamination



Data regarding the monitoring of acrolein are available for ambient and indoor air. Data from the EPA National Air Quality System show average acrolein concentrations in ambient air in the United States ranging between 0.5 and 3.186 ppbv (ppb based on volume) (EPA 2004a). For indoor air, acrolein concentrations range from <0.05 to 29 µg/m^3 (<0.02–12 ppb), with the higher concentrations in this range typically being obtained from indoor environments where the combustion of tobacco products occurs (CARB 1992; Highsmith and Zweidinger 1988; WHO 2002).

No data indicated that acrolein is a contaminant of drinking water supplies. The EPA STORET data indicate that acrolein occurs at a low frequency in waste water streams, ambient surface water, and groundwater in the United States. Acrolein has been detected in surface water and groundwater samples collected offsite at 4 and 15 of the 31 hazardous waste sites, respectively, where acrolein has been detected in some environmental medium (HazDat 2005). The HazDat information includes data from both NPL and other Superfund sites. Concentrations of acrolein in landfill leachate ranged from 2.1 to 234 ppm. In groundwater, the concentrations of acrolein ranged from 1.3 to 75 ppm with the highest concentrations generally obtained from onsite monitoring wells (HazDat 2005). Acrolein is intentionally introduced into irrigation canal and other waterways to control underwater plants and other aquatic life. In 2001, 239,362 pounds (120 tons) of acrolein were used for this purpose in California (EPA 2003). Information on the quantities of acrolein that are released into waterways as a pesticide was not available for other U.S. states.

Acrolein is a gaseous constituent of cigarette smoke and has been detected at levels equivalent to 3–220 µg per cigarette. Acrolein is formed when fats are heated to high temperatures. It has also been found in foods and food products such as raw cocoa beans, volatiles from cooked mackerel and white bread, and vegetable oils, wine, whiskey, and lager beer. Acrolein concentrations in food are typically under 40 µg/g, with most concentrations at 1 µg/g or less (WHO 2002). Acrolein can be produced endogenously as a product of lipid peroxidation (Uchida et al. 1998a, 1998b) and can form protein adducts that have been implicated in atherosclerosis and Alzheimer's disease.

Monitoring data indicate that the general population may be exposed to acrolein through inhalation of contaminated air and through ingestion of certain foods. Other than exposures to acrolein through the inhalation of tobacco smoke, another important source of acrolein exposure may be via the overheating of fats contained in all living matter. Because of the lack of recent, comprehensive monitoring data the average daily intake of acrolein through the consumption of food and drinking water, and the relative importance of each of these sources of exposure, cannot be adequately determined. Estimating the typical

level of exposure to acrolein is complicated because acrolein is a common component of tobacco smoke, and there is wide variation among individuals regarding the frequency and level of exposure to tobacco smoke. Even so, estimates of acrolein exposure in both the general population and for nonsmokers living with a resident smoker are available. A study from Environment Canada (2000) suggests that the general population is exposed to an average acrolein concentration of 1.3 μg/m^3 with a median value of 0.6 μg/m^3. Based on this average acrolein exposure and an inhalation volume of 20 m^3, it can be estimated that the average adult inhales 26 μg acrolein/day. Nazaroff and Singer (2004) estimated that the daily average inhalation intake of acrolein through environmental tobacco smoke (ETS) over the lifetime of a nonsmoker is 22–50 μg/day for males and 16–36 μg/day for females. These exposure levels for nonsmokers in a household with ETS are approximately 2.2–3.7 times higher than residents living within a household without ETS.

There is potential for exposure to acrolein in many occupational settings as the result of its varied uses and its formation during the combustion and pyrolysis of materials such as wood, petrochemical fuels, and plastics. As a result, it would be difficult to list all the occupations in which work-related exposure to acrolein occurs. It appears that occupational exposure can occur via inhalation and dermal contact.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

6.2.1 Air

Estimated releases of 0.27 million pounds (120 metric tons) of acrolein to the atmosphere from 41 domestic manufacturing and processing facilities in 2002, accounted for about 66% of the estimated total environmental releases from facilities required to report to the TRI (TRI02 2005). These releases are summarized in Table 6-1.

Potential sources of atmospheric release of acrolein include: emissions from facilities involved in the manufacture or use of products containing acrolein; volatilization from treated waters and contaminated waste streams; formation as a photooxidation product of various hydrocarbon pollutants such as propylene, 1,3-butadiene, and other diolefins; emissions from combustion processes; and use in petroleum operations (Eisler 1994; Graedel et al. 1978; Guilarducci and Tjeerdema 1995; Maldotti et al. 1980; WHO 1991, 2002).

Specific combustion sources include exhaust gas from engines powered by gasoline, diesel or other petrochemical fuels, power plants, burning vegetation (i.e., forest fires), combustion of cellulose materials such as wood, cotton, tobacco, and marijuana, and combustion of polyethylene plastics (EPA 1998a; 1998b; Hodgkin et al. 1982; Jonsson et al. 1985; Lipari et al. 1984; WHO 1991, 2002).

Acrolein is also a pyrolysis product of polyethylene, animal fats and vegetable oils, cellophane, plastics, and paraffin wax (Boettner and Ball 1980; EPA 1980; Potts et al. 1978; Tanne 1983; Wharton 1978). The concentrations of acrolein in emissions from various combustion and pyrolysis processes are listed in Table 6-2.

Recent estimates of the atmospheric loading rate of acrolein from a number of sources in the United States are available. Based on a report on national air pollutant emission trends for 1990–1993, it is estimated that total emissions of acrolein in the United States from all sources was 62,660 tons/year (EPA 1998a). The major sources of acrolein emissions were attributed to mobile (12,271 tons/year) and unspecified stationary (49,400 tons/year) combustion sources. The mobile source emission estimates for acrolein were subdivided into 5,541 tons/year for highway (e.g., automobiles, trucks, buses, and motorcycles) and 6,729 tons/year for off-highway (e.g., airplanes, boats, railway engines, lawnmowers, and off-road vehicles) combustion sources.

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Acrolein[a]

		Reported amounts released in pounds per year[b]						
						Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	On-site[j]	Off-site[k]	On- and off-site
AL	1	61	No data	0	0	61	0	61
AR	1	0	No data	0	0	0	0	0
CA	1	114	0	0	0	114	0	114
GA	3	89,310	1,500	0	0	90,810	0	90,810
IA	1	250	No data	0	0	250	0	250
IL	2	24,370	No data	0	0	24,370	0	24,370
KS	3	7,430	No data	0	0	7,430	0	7,430
LA	3	2,531	0	0	0	2,531	0	2,531
MI	2	1,705	No data	0	0	1,705	0	1,705
MN	1	20,545	No data	0	0	20,545	0	20,545
MS	2	73,865	No data	0	0	73,865	0	73,865
NE	1	2,017	No data	0	0	2,017	0	2,017
OH	1	255	No data	460	0	715	0	715
SD	1	3,159	No data	0	0	3,159	0	3,159
TN	1	3	No data	0	0	3	0	3
TX	16	36,200	0	135,053	10	170,823	440	171,263
WI	1	3,900	No data	0	0	3,900	0	3,900
Total	41	265,716	1,500	135,513	10	402,299	440	402,739

Source: TRI02 2005 (Data are from 2002)

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Table 6-2. Acrolein in Emissions from Combustion

Source	Concentration	References
Auto exhaust gas		
Gasoline engine	Not detected to 27.7 ppm (detection limit 0.01 ppm); 0–7.79% of total aldehydes, excluding acetone	IARC 1995; Lipari and Swarin 1982; Nishikawa et al. 1987a; Seizinger and Dimitriades 1972; Sigsby et al. 1987; Zweidinger et al. 1988
Gasoline engine	0.16 mg/L gasoline	Grosjean et al. 2001
Diesel engine	2.26 mg/L diesel fuel	
Diesel engine	0.05–0.3 ppm	IARC 1985, 1995; Seizinger and Dimitriades 1972
Ethanol engine	Not detected (detection limit 0.01 ppm)	Lipari and Swarin 1982
Cigarette smoke	3–220 µg/cigarette	Dong et al. 2000; Guerin et al. 1987; Hoffman et al. 1975; Horton and Guerin 1974; Lau et al. 1997; Magin 1980; Manning et al. 1983
Marijuana smoke	92–145 µg/cigarette	Hoffman et al. 1975; Horton and Guerin 1975
Smoke		
Wood	50 ppm	Einhorn 1975
Cotton	60 ppm	
Kerosene	<1 ppm	
Emissions from woodburning fireplaces	21–132 mg/kg wood 20–103 mg/kg wood	Lipari et al. 1984 EPA 1993x
Softwood	46.90 mg/kg wood	McDonald et al. 2000
Hardwood	91.23 mg/kg wood	
Hardwood, wood stove	45.54 mg/kg wood	
Emissions from power plants:		
Coal-fueled	0.002 pounds of aldehydes/ 1,000 pounds of fuel	Natusch 1978
Gas-fueled	0.2 pounds of aldehydes/ 1,000 pounds of fuel	
Oil-fueled	0.1 pounds of aldehydes/ 1,000 pounds of fuel	
Pyrolysis of polyvinyl chloride food-wrap film during hot wire cutting	27–151 ng/cut	Boettner and Ball 1980
Emissions from the combustion of polyethylene foam	2–23	Potts et al. 1978
Pyrolysis of polyethylene foam	76–180 ppm	Potts et al. 1978
15 cm above heated cooking oil	2.5–30 mg/m^3	EPA 1980b
Emissions from burning candle	0.18 µg/kg	Lau et al. 1997

Mobile source emissions of acrolein into air for the 48 contiguous states were estimated to be 30,619 tons/year in 1996 (EPA 2001). This estimate is based on data obtained from the 1996 National Toxics Inventory. The emissions were divided out into onroad (23,393 tons/year) and nonroad (7,226 tons/year) sources. Projected estimates of acrolein emissions in 2007 for onroad and nonroad sources were 11,203 and 5,019 tons/year, respectively. The projections assume a 30 ppm cap on sulfur in gasoline nationwide and implementation of Tier 2 mobile source exhaust emissions standards for light duty vehicles, but do not account for a phase-out of methyl tert-butyl ether (MTBE) in the reformulated gasoline program. Tables 6-3 and 6-4 provide specific release data based on the type of onroad and nonroad mobile sources, respectively. The major onroad acrolein emissions are generated from light duty gasoline vehicles and light duty gasoline trucks. The major generators of acrolein emissions from nonroad sources are nonroad diesel vehicles and airports.

Production of acrolein in air is known to occur through photochemical reactions of volatile organic compounds (VOCs) that are released from a number of differing source types, including solvent and fuel vapors and automobile exhaust (Ghilarducci and Tjeerdema 1995; Liu et al. 1999a; 1999b). Harley et al. (1994) estimated a total daily production of 4,600 kg/day for acrolein from both source emissions and photochemical production in air over the Los Angeles area for August 1987. The estimate is derived from a photochemical air quality model that tracks the transport and chemical reactions of selected VOCs and uses emission rates of carbon monoxide, nitrogen oxides, and VOCs from 800 source types prepared by the California Air Resources Board and the South Coast Air Quality Management District. Based on the modeling, the contribution of direct emissions and photochemical production to the total acrolein emissions are roughly similar. The model also shows that the total daily production rate of 4,600 kg/day results in a predicted range of 1.1–2.1 ppb carbon for the concentration of acrolein in air over the Los Angeles region.

Emissions of acrolein from coal-fired electric utility steam plants in the United States were estimated to be 27 tons/year in 1994 (EPA 1998b). This estimate was based on emission data obtained from 52 of 684 utility plants that were considered to be generally representative of the industry. Acrolein emissions of 34 tons/year were estimated for the year 2010 and are based on projected increases in electrical power usage and changes in fuel choices. However, the projections used to derive the 2010 estimate do not account for factors such as industry restructuring, new particulate and ozone standards, or global climate change programs.

Table 6-3. Estimated Acrolein Emissions from Onroad Mobile Sources in 1996 and 2007[a]

	Acrolein emissions (tons/year)							
Year	LDGV	LDGT	HDGV	MC	LDDV[b]	LDDT	HDDV	Total
1996	10,682	8,822	1,756	281	164	84	1,604	23,393
2007	3,044	5,444	687	363	0	16	1,649	11,203

[a]EPA 2001
[b]LDDV usage is expected to be phased out by 2007.

HDDV = heavy duty diesel vehicles; HDGV = heavy duty gasoline vehicles; LDDT = light duty diesel trucks; LDDV = light duty diesel vehicles; LDGT = light duty gasoline trucks, categories 1 and 2; LDGV = light duty gasoline vehicles; MC=motorcycles

Table 6-4. Estimated Acrolein Emissions from Nonroad Mobile Sources in 1996 and 2007[a]

	Acrolein emissions (tons/year)						
Year	2-Stroke gasoline	4-Stroke gasoline	Nonroad diesel	Marine diesel	Railroad	Airports	Total
1996	511	470	4,996	77	167	1,006	7,226
2007	385	297	2,836	84	139	1,277	5,019

[a]EPA 2001

Emissions of acrolein into air from paper and wood product manufacturing in Canada have been estimated for the year 1995. Acrolein emissions ranged from 3,208 to 25,664 kg/year (3.544–28.289 tons/year) for oriented strand board producers and from 3,747 to 18,735 kg/year (4.130–20.651 tons/year) for pulp and paper (kraft) mills (WHO 2002).

The intentional release of acrolein into irrigation channels as an herbicide and molluscicide also results in the volatilization of acrolein into air (Eisler 1994; EPA 2003; Ghilarducci and Tjeerdema 1995). In the San Joaquin Valley of California, it was reported that 194,668 pounds (97.3 tons) of acrolein were emitted into the air from agricultural uses of the pesticide in 2001, which amounted to 1.4% of the total pesticide emissions from this region (CEPA 2002).

Anderson (1983) estimated the total loading rate of acrolein in 1978 for the United States to be 91,450 pounds (45.7 tons) from facilities involved in its production and use as a chemical intermediate. Loading rates of acrolein into the environment from various industrial sources were as follows: acrylic acid manufacturers, 15,175 pounds (7.59 tons); refined acrolein and glycerin manufacturers, 55,660 pounds (27.8 tons); methionine manufacturers, 18,150 pounds (9.08 tons); and miscellaneous intermediate uses, 2,420 pounds (1.21 tons). These loading rates were based on a total production volume of 350 million pounds (175,000 tons) for acrolein with 87% of this volume consumed in the production of acrylic acid and its derivatives.

6.2.2 Water

Estimated releases of 1,500 pounds (0.7 metric tons) of acrolein to surface water from 41 domestic manufacturing and processing facilities in 2002, accounted for about 0.4% of the estimated total environmental releases from facilities required to report to the TRI (TRI02 2005). These releases are summarized in Table 6-1.

Acrolein may be released to water in effluents from its manufacturing plants and use facilities (see Section 5.3 for specific information regarding uses) and from its direct application to water as a broad-range biocide in irrigation canals, cooling towers, water treatment basins, and process water circuits (Eisler 1994; EPA 2003; Ghilarducci and Tjeerdema 1995; IARC 1985; Lue-Hing et al. 1981; WHO 1991; WSSA 1983).

The amount of acrolein released from industrial operations to publicly owned treatment works (POTW) in the U.S. waters in 1986 was estimated to be 1,645,600 pounds/year (823 tons/year) (EPA 1991). However, it is reported that a large portion of the acrolein that is received by POTWs is removed before discharge in effluent streams, with 5% released to surface waters, 0–5% to air, and 10% to sludge (EPA 1991).

Data on the release of acrolein into water as a consequence of its use as a pesticide are available only for the state of California. It is reported that usage of acrolein in California declined from 328,238 pounds (164 tons) in 1999 to 290,180 pounds (145 tons) and 233,928 pounds (117 tons) in 2000 and 2001, respectively (EPA 2003). The predominant use of acrolein is as an aquatic herbicide with releases into rights-of-way (i.e., irrigation canals) and other water areas amounting to 326,767 pounds (163 tons), 297,320 pounds (149 tons), and 239,362 pounds (120 tons) in 1999, 2000, and 2001, respectively. The decrease in acrolein usage is due to changes in the permitting process required prior to acrolein treatment of irrigation canals instituted in 2001. Once irrigation districts in California work through the new permitting process, it is expected that future usage of acrolein will be comparable to acrolein usage reported for 1999–2000.

6.2.3 Soil

Estimated releases of 10 pounds (0.005 metric tons) of acrolein to soils from 41 domestic manufacturing and processing facilities in 2002, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI02 2005). An additional 0.13 million pounds (61 metric tons), constituting about 34% of the total environmental emissions, were released via underground injection (TRI02 2005). These releases are summarized in Table 6-1.

The occurrence of acrolein in soil at one hazardous waste site in the United States and leachate from several municipal landfills provides evidence that this compound has been released to soil as the result of land disposal of some organic wastes. No data were located regarding the amount of acrolein released to soil.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Acrolein is relatively unstable in the atmosphere; therefore, transport within the atmosphere is expected to be limited. The relatively high vapor pressure of acrolein (274 mm Hg at 25 °C [Daubert and Danner 1987]) suggests that this compound will not partition from the vapor phase to particulates in the atmosphere. Occurrence of acrolein in rainwater (Grosjean and Wright 1983; Nishikawa et al. 1987b) indicates that this compound may be removed from the atmosphere by washout.

Volatilization is expected to be a significant removal process for any acrolein released to surface waters. Based on a measured Henry's Law constant of 1.22×10^{-4} atm-m^3/mol at 25 °C (Gaffney et al. 1987), the volatilization half-life from a model river 1 m deep, flowing 1 m/set with a wind speed of 3 m/sec was estimated to be 23 hours using the method of Thomas (1982). Veith et al. (1980) measured a bioconcentration factor (BCF) of 344 for acrolein in bluegill sunfish; however, this may be an overestimate, since total 14C was measured in the fish, which may have resulted in the measurement of acrolein metabolites. A BCF of 0.6 was estimated for acrolein using a linear regression equation based on a log octanol/water partition coefficient (K_{ow}) of -0.01 (Bysshe 1982; Hansch and Leo 1985). These BCFs, as well as the relatively high water solubility of this compound, suggest that acrolein does not bioconcentrate significantly in aquatic organisms. Acrolein did not accumulate in leaf lettuce after both single and multiple applications in irrigation water at a concentration of 75 ppm (Nordone et al. 1997). Acrolein residues in the lettuce fell to 0% within 53 days following the initial application.

Using a linear regression equation based on log K_{ow} data (Lyman 1982), an adsorption coefficient (K_{oc}) of 24 was estimated, which suggests that adsorption of acrolein to suspended solids and sediments in water would not be significant. This does not take into account the reactivity of acrolein which could lead to the removal of acrolein from water through chemical binding of the compound to dissolved or suspended organics in water and sediments. Irwin (1988) reports a range of experimental K_{oc} of 51–270 for adsorption of acrolein to two soils. The relatively low experimental and estimated K_{oc} values suggest that acrolein will be highly to moderately mobile in soil and that this compound has the potential to leach significantly (Swann et al. 1983). However, the adsorption of acrolein to soil has been shown to be irreversible (Irwin 1988). Irreversible sorption, biodegradation, hydration, and volatilization of acrolein in soil can be expected to significantly retard the leaching of acrolein through soil.

The relatively high vapor pressure of acrolein and its volatility from water suggest that this compound will evaporate rapidly from soil surfaces and that volatilization is probably a major removal process from soil. The relatively low K_{oc} value for acrolein indicates high mobility in soil and suggests that this compound has the potential to leach significantly (Swann et al. 1983). Degradation processes and volatilization, however, are expected to significantly retard movement of acrolein through soil.

6.3.2 Transformation and Degradation

6.3.2.1 Air

The dominant removal process for acrolein in ambient air is predicted to be reaction with photochemically generated hydroxyl radicals in the troposphere. The atmospheric half-life for acrolein is estimated to be 15–20 hours, based on experimentally determined hydroxyl radical reaction rate constants ranging between 1.90×10^{-11} and 2.53×10^{-11} cm^3/molecules-sec at 25–26 °C and an average ambient hydroxyl radical concentration of 5.0×10^5 molecules/cm^3 (Atkinson 1985). Acrolein reacts with hydroxyl radicals as both an olefin and an aldehyde (Grosjean 1990). Products of this reaction include carbon monoxide, formaldehyde, glyoxal, and glycolaldehyde. In the presence of nitrogen oxides, products include peroxynitrate, nitric acid, glycidaldehyde, malonaldehyde, and 3-hydroxypropanaldehyde (Edney et al. 1986; Grosjean 1990; Liu et al. 1999b).

Direct photolysis in the ambient atmosphere occurs but is expected to be of minor importance. Gardner et al. (1987) reported that the quantum yields for irradiation of acrolein at low air pressures were 0.0066 at 313 nm and 0.0044 at 334 nm. The authors used a computer analysis of their photodissociation data to estimate the half-life of acrolein to be 10 days in the lower troposphere and <5 days in the upper troposphere.

Experimental data indicate that reaction of acrolein with ozone ($k=2.8 \times 10^{-19}$ cm^3/molecules-sec at 25 °C; half-life, 59 days) or nitrate radicals ($k=5.9 \pm 2.8 \times 10^{-16}$ cm^3/molecules-sec at 25 °C; half-life, 16 days) in the troposphere would be too slow to be environmentally significant (Atkinson 1985; Atkinson et al. 1987). The fate of acrolein in indoor air is expected to be different from its fate in outdoor air because of differences in the concentrations of oxidants in indoor air compared to outdoor air and the possibility of other mechanisms of removal.

6.3.2.2 Water

Low concentrations of acrolein may degrade in natural water by either aerobic biodegradation or reversible hydration to β-hydroxypropionaldehyde, which subsequently undergoes aerobic biodegradation (Bowmer and Higgins 1976; Callahan et al. 1979; Ghilarducci and Tjeerdema 1995; Tabak et al. 1981). Acrolein at a concentration of 5–10 mg/L was completely degraded in 7–10 days in a static culture flask screening procedure (Tabak et al. 1981). Acrolein applied to surface waters at application rates suggested for herbicidal use can persist up to 6 days (WSSA 1983). Bowmer and Higgins (1976) measured acrolein removal in both laboratory water and in field experiments using irrigation channels. Their studies suggested that the degradation of the hydration product of acrolein, 3-hydroxypropanal, occurs after the concentration of acrolein falls below 2–3 ppm. The degradation of 3-hydroxypropanal was also preceded by a 100-hour lag period, suggesting that biodegradation was occurring through the action of acclimated cultures.

In buffered laboratory water, acrolein reached its equilibrium apparently with β-hydroxypropionaldehyde in approximately 300 hours (92% β-hydroxypropionaldehyde, 8% acrolein); in irrigation channels, acrolein removal was complete. Half-lives were reportedly <1–3 days in surface water, but values were for the combined effect of degradation and volatilization (Bowmer and Higgins 1976; Bowmer et al. 1974). Kissel et al. (1978) measured acrolein removal in buffered laboratory water and natural river water using both chemical analysis methods and bioassays. Complete hydrolysis (which according to the authors includes hydration to 3-hydroxypropanal) occurred within 150, 120–180, and 5–40 hours in buffered solutions at 22 °C and pH 5, 7, and 9, respectively. Based on fish kill bioassays in natural river water at pH 8.1, >93% degradation of acrolein occurred within 6 days. The half-lives of acrolein in aerobic test systems that were treated at an application rate of 15 mg/L were 9.5 hours in water and 7.6 hours in sediment (Smith et al. 1995). The half-lives of acrolein in anaerobic test systems treated at the same rate were 10.3 hours in water and approximately 10 days in sediment. Degradation products included 3-hydroxypropanal, acrylic acid, and allyl alcohol, which indicate that both hydrolysis and biodegradation contributed to the degradation of acrolein during this study.

Jacobson and Smith (1990) studied the dissipation of acrolein, applied at the highest recommended rate according to the label, to achieve a 15 ppm concentration for a 2-hour duration in an irrigation canal and a lateral of the canal, which was infested with aquatic plants. The dissipation half-lives for acrolein in the irrigation and lateral canals were 275 and 64 minutes, respectively. No acrolein residues were detected (detection limit, 0.01 ppm). No residues of 3-hydroxypropanal were detected (detection limit, 2.0 ppm) in

any of the water samples from either canal. These data suggest that acrolein will not persist for moderate or long periods of time in aerobic aquatic environments and that hydration of acrolein may not be an important degradation pathway for acrolein (Jacobson and Smith 1990). The decay rate constants for acrolein applied to irrigation canals have been reported to be similar (0.14–0.21) regardless of the difference in time-concentration regimens (100 µg/L for 48 hours to 15,000 µg/L for several hours) (Eisler 1994). The half life of acrolein, applied at a flow rate of 3,964 L/second to achieve 15 ppm for 1 hour, was 10.2 hours in a weedy canal and 7.3 hours in a nonweedy canal (Nordone et al. 1996; Rathbun 1998). The concentration of acrolein was 25 µg/L in samples from the Columbia River collected 65 km from where it was applied at a concentration of 125 µg/L (Eisler 1994).

The ultraviolet (UV) spectrum of acrolein in hexane shows moderate absorption of UV light in the environmentally significant range (wavelengths >290), suggesting that acrolein might undergo photolysis in natural waters; however, hydration of acrolein destroys the chromophores that absorb UV light (Callahan et al. 1979), and the equilibrium appears to be far on the side of the hydration product. Thus, the potential for direct photolysis of acrolein in natural waters is probably slight. Oxidation of small amounts of acrolein in natural waters would not be environmentally significant; however, highly concentrated acrolein solutions (i.e., spills) may be polymerized by oxidation or hydration processes (Callahan et al. 1979). Insufficient data are available regarding anaerobic biodegradation to establish the significance of this process as a removal mechanism or to determine the rate at which such a process would proceed. This information would be particularly useful in determining the fate of acrolein under conditions frequently encountered in groundwater and in landfills.

Based on the reactivity and nucleophilicity of acrolein, it is expected that acrolein has the potential to react with dissolved and suspended organics in water. This removal process would become increasingly important for determining the fate of acrolein in water as the concentration of organics in water increased. However, no studies have been conducted to describe this possible route for removal of acrolein from water.

6.3.2.3 Sediment and Soil

Experimental data specifically pertaining to the degradation or transformation of acrolein in soil were not located. Results of studies in aquatic systems suggest that acrolein, at low concentrations, may be subject to aerobic biodegradation in soil or transformation via hydration followed by aerobic biodegradation of the hydrated product (see Section 6.3.2.2).

Since acrolein is a very reactive compound, abiotic processes, such as oxidation or conjugation with organic matter in soils, may be the most important degradation processes. However, no information could be located for these possible acrolein reaction pathways in soil.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to acrolein depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of acrolein in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on acrolein 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 acrolein in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

The atmospheric concentrations of acrolein have been measured in several locations, and the most comprehensive monitoring studies are discussed below. Data for 2004 obtained from EPA's Air Quality System (AQS) database show average concentrations of acrolein at various monitoring stations ranging from 0.3 to 2.048 ppb carbon (0.5–3.186 ppbv), with maximum values ranging from 0.3 to 3.6 ppb carbon (0.5–5.6 ppbv) (EPA 2004a). Data obtained for 1996 show similar average concentrations for acrolein, ranging from 0.05 to 3.2 ppb carbon (0.08–5.6 ppbv) with maximum values ranging from 0.5 to 11.46 ppb carbon (0.8–17.82 ppbv). Lower average concentrations of 0.05–0.64 ppb carbon (0.08–1.00 ppbv) for acrolein (maximum values ranging from 0.05 to 9.9 ppb carbon [0.08–15 ppbv]) were found for 2000. The National Air Toxics Monitoring Program (EPA) reported peak concentrations for acrolein of <1 ppbv at 12 monitoring sites, with one site reporting a peak concentration between 1 and 5 ppbv (Mohamed et al. 2002). These data were obtained in 1996 at 13 monitoring sites in New Jersey, Louisiana, Texas, and Vermont.

In the National Air Quality and Emissions Trend Report for 1998, the concentrations of acrolein in ambient air averaged 0.20 and 0.12 μg/m^3 (0.086 and 0.052 ppb) for urban and rural locations, respectively, based on emission and monitoring data obtained in 1996 (EPA 1998c). In the report

submitted for 1999, it was noted that during the period of 1994–1999, the concentrations of acrolein are either showing no trend or are trending upwards in concentration in six urban areas (EPA 1999). Information on trends in acrolein concentrations in rural areas was available for only one rural location, showing a downward trend within the same time period.

A concentration of acrolein in ambient air in California has been estimated to average 0.36 μg/m^3 (0.16 ppb) and is based on emissions and census tract data obtained in 1999 (Morello-Frosch et al. 2000). Estimated concentrations of acrolein in ambient air for the San Francisco Area in 1990–1991 ranged from 0.012 to 0.28 μg/m^3 (0.005–0.12 ppb) (Rosenbaum et al. 1999). Ambient air concentrations of acrolein at the Oakland-San Francisco Bay Bridge Toll Plaza obtained in April 2001 showed differing concentrations between morning and evening measurements. Acrolein concentrations ranged from 0.096 to 0.140 μg/m^3 (0.041–0.060 ppb) during the morning commute, which were lower than the concentrations of 0.031–0.047 and 0.058–0.079 μg/m^3 (0.013–0.020 and 0.025–0.034 ppb) during two evening monitoring periods taken on consecutive days (Destaillats et al. 2002). Altshuller and McPherson (1963) and Renzetti and Bryan (1961) determined that acrolein levels in air samples collected in Los Angeles, California, during 1960–1961 averaged between 5 and 8 ppb. Air samples collected in the Los Angeles Basin over a 12-week period during 1968 contained levels ranging between none detected to 18 ppb, although most values ranged between 0.9 and 9 ppb (IARC 1985).

Acrolein has been detected in indoor air and its concentrations are summarized in Table 6-5. The concentrations of acrolein range from <0.05 to 29 μg/m^3 (<0.02–12 ppb) in residential homes (CARB 1992; Highsmith and Zweidinger 1988; WHO 2002). Acrolein concentrations are found to be typically higher in indoor air when comparing paired indoor/outdoor samples taken at a site (CARB 1991; WHO 1991, 2002)

Acrolein has been detected in air samples collected at 5 of the 31 hazardous waste sites where acrolein has been detected in some environmental medium (HazDat 2005). The HazDat information includes data from both NPL and other Superfund sites. Concentrations of acrolein in outdoor air ranged from 0.03–6 to 0.013–42.4 ppbv in onsite and offsite sampling, respectively (HazDat 2005).

6.4.2 Water

Data from the EPA STORET Data Base indicate that acrolein has a low frequency of occurrence in waste water streams, ambient surface water, and groundwater in the United States (EPA 1988b; Staples et al.

Table 6-5. Acrolein Concentrations in Indoor Air

Type of buiilding	Concentration	Location	References
Residential	0.36–1.95 ppbv[a] (0.85–4.62 µg/m^3)[b]	Raleigh, North Carolina	Highsmith and Zweidinger 1988
Residential	NQ–29 µg/m^3[c] 7.1 µg/m^3 (average)	Woodland, California	CARB 1992
Residential	0.4–8.1 µg/m^3	Windsor, Ontario	WHO 2002
Residential	<0.05–5.4 µg/m^3	Hamilton, Ontario	
Residential	16–23 µg/m^3	Toronto, Ontario	
Restaurants	8–18 ppb (19–43 µg/m^3)[b]	Zürich, Switzerland	Weber et al. 1979
Student lounge			
Non-smoking	0.8–1.6 µg/m^3	Bounds Green, United Kingdom	Williams et al. 1996
Smoking	6.4 µg/m^3		
Tavern	21–24 µg/m^3	Research Triangle Park, North Carolina	Löfroth et al. 1989

[a]ppbv = parts per billion by volume
[b]Converted measurement in ppbv to µg/m^3, assuming an ambient temperature of 20 °C and an atmospheric pressure of 1,013 mbars.
[c]NQ = not quantifiable below detection limit of 2.0 µg/m^3

1985). Acrolein has not been found as a contaminant of drinking water (EPA 1980; Krill and Sonzogni 1986; Otson 1987; WHO 2002). Grosjean and Wright (1983) detected acrolein, in combination with acetone, at a concentration of 0.05 µg/mL (50 ppb) in rain water collected in Los Angeles, California; however, these compounds were not detected in rain water samples collected in four less densely populated sites in California.

More recently, acrolein has been detected in surface water and groundwater samples collected at 4 and 15 of the 31 hazardous waste sites, respectively, where acrolein has been detected in some environmental medium (HazDat 2005). The HazDat information includes data from both NPL and other Superfund sites. Concentrations of acrolein in landfill leachate ranged from 2.1 to 234 ppm (HazDat 2005; Sabel and Clarke 1984). In groundwater, the concentrations of acrolein ranged from 1.3 to 75 ppm with the highest generally obtained from onsite monitoring wells (HazDat 2005).

6.4.3 Sediment and Soil

Acrolein was identified in sediment/ soil/water samples collected from Love Canal in Niagara Falls, New York (Hauser and Bromberg 1982); however, no quantitative data were available.

More recently, acrolein has been detected in soil and sediment samples collected at 1 and 2 of the 31 hazardous waste sites, respectively, where acrolein has been detected in some environmental medium (HazDat 2005). The HazDat information includes data from both NPL and other Superfund sites. One soil sample site was found to have an acrolein concentration of 100 ppm (HazDat 2005).

6.4.4 Other Environmental Media

Acrolein can be produced in endogenously as a product of lipid peroxidation (Uchida et al. 1998a, 1998b) and can form protein adducts that have been implicated in atherosclerosis (Uchida et al. 1998b) and Alzheimer's disease (Calingasan et al. 1999). Acrolein has been identified in foods and food components such as raw cocoa beans, chocolate liquor, souring salted pork, fried potatoes and onions, raw and cooked turkey, and volatiles from cooked mackerel, white bread, raw chicken breast, ripe Arctic bramble berries, heated animal fats and vegetable oils, and roasted coffee (Cantoni et al. 1969; EPA 1980, 1985; Feron et al. 1991; IARC 1985; Umano and Shibamoto 1987). Feron et al. (1991) reported concentrations of acrolein of <0.01–0.05 ppm in various fruits and up to 0.59 ppm in cabbage, carrots, potatoes, and

tomatoes. The concentration in food is <40 µg/g and, in most instances, is <1 µg/g (WHO 2002). The acrolein concentrations in heated fats and oils and in the headspace above these materials increase with increasing cooking temperature (Casella and Contursi 2004; Ghilarducci and Tjeerdema 1995; WHO 2002). For example, peanut oil heated for 2 hours at 110, 145, and 200 °C resulted in the production of acrolein at concentrations of 0.2, 2.7, and 24 µM, respectively (Casella and Contursi 2004). In comparison to other oils, peanut oil was found to have the lowest production of acrolein after 2 hours of heating at 145 °C, with higher concentrations found in sunflower (2.9 µM), corn oil (4.3 µM), and olive oil (9.3 µM) when heated under the same conditions. Sufficient data are not available to establish the level of acrolein typically encountered in these foods. Trace levels of acrolein have been found in wine, whiskey, and lager beer (IARC 1985). Further information regarding the occurrence of acrolein in food and related products is provided by EPA (1980).

Acrolein is a gaseous constituent of tobacco and marijuana smoke, occurring in both mainstream and sidestream smoke (Ayer and Yeager 1982; Hoffman et al. 1968; Holzer et al. 1976; Rylander 1974; Weber-Tschopp et al. 1977). The level of acrolein in sidestream smoke has been found to be notably higher (12 times higher) than in mainstream smoke (Triebig and Zober 1984). The amount of acrolein emitted in tobacco smoke varies depending upon the kind of cigarette, smoking conditions, puff volume, puff rate, nature, and type of tobacco, as well as a number of other extraneous factors (Holzer et al. 1976). Smoke from various cigarettes has been found to contain 3–220 µg acrolein per cigarette (Dodson 1994; Hoffman et al. 1968; Horton and Guerin 1974; Magin 1980; Manning et al. 1983). Smoke from a marijuana cigarette was also found to contain 92–145 µg/cigarette (Hoffman et al. 1968; Horton and Guerin 1974). Studies performed to determine the concentration of acrolein in smoke-filled rooms (Rylander 1974; Triebig and Zober 1984; Weber-Tschopp et al. 1977) indicate that the concentration of acrolein in indoor air is highly dependent upon such factors as the number of cigarettes smoked, rate at which the cigarettes are smoked, size of the room, number of people in the room, and type of ventilation. Acrolein levels measured in various settings where people were smoking are: cafe, 30–100 ppb; train, 10–120 ppb; car with three smokers (windows open), 30 ppb (average); car with three smokers (windows closed), 300 ppb (average); restaurant, 3–13 ppb; tavern, 5–18 ppb; and cafeteria, l–10 ppb (Triebig and Zober 1984).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population may be exposed to acrolein through inhalation of contaminated air, inhalation of cigarette smoke, and through ingestion of certain foods. Widespread exposure occurs due to the

formation of acrolein during the overheating of fats. Acrolein has been detected in the vapor of rapeseed oil, which is used frequently in Chinese wok cooking (Pellizzari et al. 1995). Primary factors influencing the level of exposure to acrolein via inhalation are: location (urban versus rural), duration and frequency of exposure to tobacco smoke, concentration of tobacco smoke, duration and frequency of exposure to high concentrations of vehicle exhaust (e.g., in parking garages, in heavy traffic), occupational exposure, and downwind distance of residence or work site relative to stationary point sources. Primary factors influencing the level of exposure to acrolein via ingestion are diet and volume of intake, which is typically related to age and sex.

Because of the lack of recent comprehensive monitoring data for acrolein in water and food, the average daily intake of acrolein and the relative importance of each source of exposure cannot be determined. However, probabilistic estimates of 24-hour time-weighted concentrations of acrolein in air have been used to assess human exposures to acrolein in the Canadian population (Environment Canada 2000; WHO 2002). Mean and median estimates of acrolein concentration of 1.3 and 0.6 μg/m^3 (0.56 and 0.26 ppb), respectively, were derived, with a 95% percentile value of 5.0 μg/m^3 (2.1 ppb). The estimate uses measured data on acrolein concentrations obtained between 1989 and 1996 for outdoor air in rural, suburban, and urban sites and indoor air measurements taken in 40 homes between 1991 and 1993. The exposure estimate assumes both a mean time of 3 hours spent outdoors and that the general population is exposed to concentrations of acrolein similar to those in indoor air of their homes. Based on the mean estimate for acrolein concentration and an inhalation volume of 20 m^3 of air per day, it is estimated that an average adult will inhale 26 μg acrolein/day.

ETS is a major source of acrolein exposure for many individuals in the general population. Nazaroff and Singer (2004) estimate that in 2000, between 31 and 53 million nonsmokers in the United States were exposed to acrolein concentrations in indoor air ranging from 1.6 to 3.6 μg/m^3 in households where ETS is generated by one or more individuals residing in the same household. Between 15 and 25 million of the affected number of nonsmokers are adults. Based on the lifetime average for the volume of inspired air of 14 m^3/day for males and 10 m^3/day for females, it is estimated that the inhalation intake of acrolein through inspiration of ETS over a lifetime is 22–50 μg/day for males and 16–36 μg/day for females. Assuming that the exposure data obtained from the Canadian study (Environment Canada 2000) discussed above are representative of exposures of residents in the United States to acrolein in households without ETS, then it is estimated that the inhalation intake of acrolein for nonsmokers exposed to ETS in the residence is 2.2–3.8 times greater for both males and females than in households without ETS. This comparison is based on inhalation intakes of acrolein for males and females in non-ETS households of

18 and 13 µg/day, respectively, that are based on an estimated mean acrolein concentration in air of 1.6 µg/L taken from the Canadian study (2000) and on the average daily inhalation volumes of air for males and females given by Nazaroff and Singer (2004).

The general population is exposed to small amounts of endogenous acrolein. This endogenous acrolein is formed as a consequence of the peroxidation of lipid membranes and metabolism of α-hydroxy amino acids and polyamines (Alarcon 1970; Uchida et al. 1998a; WHO 2002). Acrolein has also been shown to be formed by phagocytes in response to infection or inflammation and as a result of the progression of Alzheimer's disease and atherosclerosis (Anderson et al. 1997; Calingasan et al. 1999; Gómez-Ramos et al. 2003; Uchida et al. 1998b). Due to the reactivity of acrolein with biomolecules, especially thiol-containing proteins and glutathione, the formation of acrolein *in vivo* has been measured as the byproducts of the reaction of acrolein with these biomolecules. These biomarkers of *in vivo* acrolein formation include acrolein-protein adducts and the urine metabolites, S-(3-hydroxypropyl)mercapturic acid and S-(2-carboxyethyl)mercapturic acid (Calingasan et al. 1999; Li et al. 2004; WHO 2002). However, studies to correlate the concentrations of these biomarkers with *in vivo* acrolein production in humans have yet to be conducted.

According to a National Occupational Exposure Survey (NOES) by NIOSH between 1981 and 1983, an estimated 1,298 workers (including 5 females) in 37 facilities in the United States are occupationally exposed to acrolein (NIOSH 1988; RTECS 2004). This is a tentative estimate and is subject to change as further information regarding trade name compounds becomes available. There is potential for exposure to acrolein in many occupational settings as the result of its varied uses and its formation during the combustion and pyrolysis of materials such as wood, petrochemical fuels, and plastics. As a result, it would be difficult to list all the occupations in which work-related exposure to acrolein occurs. Some of these occupations include those involved in the production of acrylates, methionine, perfumes, plastics, refrigerants, rubber, or textile resins (Ghilarducci and Tjeerdema 1995).

Acrolein has been detected in workplace air at a number of locations (Ahrenholz and Egilman 1983; Apol 1982; IARC 1985; Tharr and Singal 1986; Trietman et al. 1980; Woskie et al. 1988). Acrolein concentrations of 0.057–0.085 ppm were detected during system testing conducted as part of a submarine overhaul in Portsmouth Naval Shipyard in Portsmouth, New Hampshire (Tharr and Singal 1986). Ahrenholz and Egilman (1983) reported >0.0044–0.18 ppm acrolein in the wire line department of Rubbermaid Inc. in Wooster, Ohio, and Apol (1982) reported >0.06 ppm in molding areas of Gerlinger Casting Corp. in Salem, Oregon.

The concentrations of acrolein were 0.01 mg/m^3 (0.004 ppm) in the air of a food factory, 0.59, 0.31, 0.15, 0.16, and 0.06 mg/m^3 (0.25, 0.13, 0.064, 0.069, and 0.026 ppm) in the air of five restaurant kitchens, and 0.02 mg/m^3 (0.009 ppm) in the air of two bakeries (Vainiotalo and Matveinen 1993). Henriks-Eckerman et al. (1990) reported acrolein was emitted from coated steel plates heated to 350 °C. This indicates that workers involved in welding or heating painted metal may be exposed to acrolein

Firefighters are at risk to exposure to acrolein when battling house fires and wild fires (Ghilarducci and Tjeerdema 1995; Gochfeld 1995; Lees 1995; Materna et al. 1992). The concentrations of acrolein measured in a NIOSH house fire study ranged from not detected to 3.2 ppm, with half of the exposures exceeding the 0.3 ppm short-term exposure limit. During a study of over 224 structural fires, firefighters were exposed to acrolein at levels as high as 6.9 mg/m^3 (2.3 ppm) (Ghilarducci and Tjeerdema 1995). The concentration of acrolein in a single sample collected during a wildfire was reported to be 0.23 ppm (Lees 1995; Materna et al. 1992).

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. 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 spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

For children living in a residence where one or more individuals smokes some form of tobacco product, long-term exposure to environmental tobacco smoke (ETS) and the compounds therein are expected, which can cause a number of health effects (WHO 1999). Consequently, because of the acrolein content in ETS it is expected that the largest source of acrolein exposure for children living with a smoker is through inhalation of ETS. Information on exposures of acrolein through ETS that are specific for

children living in the United States could not be identified. However, based on data obtained from Nazaroff and Singer (2004), it is estimated that individuals who do not smoke over their lifetimes but reside with one or more individuals who do smoke, will intake between 22 and 50 µg acrolein/day for males and between 16 and 36 µg acrolein/day for females through the inhalation of acrolein in ETS over their lifetimes. This amounts to 2.2–3.7 times greater exposure to acrolein for these children than for children who are not exposed to ETS over their lifetimes (see Section 6.5). For children without exposures to ETS, their main exposures to acrolein are expected to be similar to those noted for the general population in Section 6.5 in air. Estimates of the concentration in the total diet of children in the United States were not located in the available literature. Therefore, no estimate of daily acrolein intake from food can be made. Because of the lack of recent comprehensive monitoring data for acrolein in water, the average daily intake of acrolein and the relative importance of this source of exposure cannot be determined.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Those segments of the general population with potentially high exposure to acrolein from exogenic sources include people who come in frequent or prolonged contact with tobacco or marijuana smoke, people who are occupationally exposed, and people who live or work near dense traffic areas, in smoggy areas (e.g., Los Angeles), or downwind from stationary point sources. Acrolein uptake from cigarette smoke for individuals working in bars and taverns can range from 15 to 1,830 µg/day, based on an 8-hour shift, a respiration volume of 20 m^3 air per day, and a concentration range of acrolein in air of 2.3–275 µg/m^3 (IARC 1995). Individuals who work or reside near irrigation canals and other bodies of water that are undergoing treatment with acrolein to eliminate unwanted plants or aquatic life are at risk for exposure to acrolein. Individuals living near some land-fills and other waste sites may be exposed to acrolein in ambient air or drinking water. For example, acrolein has been measured at concentrations of 1.3 ppm and 4.24 ppb in groundwater obtained from private wells offsite from two NPL landfills (Agency for Toxic Substances and Disease Registry 1988; HazDat 2005).

Patients receiving oxazaphosphorine drugs, such as cyclophosphamide and ifosfamide, for their cancer treatment are at risk for exposure to acrolein, a metabolite of these drugs (Furlanut and Franceschi 2003; Kaijser et al. 1993). For example, patients receiving cyclophosphamide at a dose of 60 mg/kg body weight/day by 1-hour infusion for 2 consecutive days had peak blood acrolein concentrations ranging between 6.2 and 10.2 µM (Ren et al. 1999). The urinary clearance of acrolein from blood during therapy results in concentrations of acrolein in urine ranging from 0.3 to 406.8 nM, depending on urine volume

(Takamoto et al. 2004). This range of urinary acrolein concentrations is sufficient to result in acrolein-induced urotoxicities that must be reduced through increasing urine volume during treatment with diuretics or receiving uroprotective drugs during treatment (Kaijser et al. 1993).

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 acrolein 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 acrolein.

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. Physical and chemical property data are essential for estimating the partitioning of a chemical in the environment. Physical and chemical property data are available for acrolein and are sufficient for estimating the environmental fate of acrolein (Amoore and Hautala 1983; Daubert and Danner 1987; Gaffney et al. 1987; Hansch and Leo 1995; HSDB 2005; Irwin 1988; Lewis 1997; Lide 2000; O'Neil 2002; Seidell 1941; Tomlin 2003; Verschueren 2001).

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2002, became available in May of 2004. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Data regarding the production methods for acrolein, production facilities, use, and disposal are adequate (Etzkorn et al. 2002; SRI 2004). Data regarding current gross estimates of production volumes and capacities are available (Arntz et al. 2002; EPA 1989b; Etzkorn et al. 2002; Hess et al. 1978; HSDB 2005; IARC 1995; IUR 2002; Lewis 1997; OHM-TADS 1988; O'Neil 2001; TRI02 2005; Windholz 1983). Production data may be difficult to obtain, since many companies desire to maintain their confidentiality. Information regarding import/export of acrolein could not be located. Data regarding release of acrolein into air are available for mobile and stationary sources (Anderson 1983; CEPA 2002; EPA 1998a, 1998b, 2001; WHO 2002). Harley et al. (1994) estimated the the relative contributions of source emissions and photochemical production of acrolein to the amount of acrolein in the air over Los Angeles. However, estimates could not be located on the contribution of photochemical production of acrolein to arcolein concentrations in the ambient air in other regions of the United States, nor were data available on the expected seasonal variations in photochemical production of acrolein. Limited data are available on the release of acrolein to publically owned treatment works and the release of acrolein as a pesticide to irrigation waters in California (EPA 1991, 2003), but no data could be located on release of acrolein to soil. Use, release, and disposal information is useful for determining where environmental exposure to acrolein may be high. Determining the percentage of acrolein used as a captive intermediate (i.e., consumed in closed processes in which the compound is not isolated) rather than as an isolated, refined product is important in estimating the amount of release to the environment from stationary, noncombustion-related sources. An estimate of the amount of acrolein released from stationary sources would be useful in establishing the relative importance of each source of acrolein. Even with the availability of information on the production, use, and disposal of acrolein, the amounts released would be difficult to estimate, since major factors contributing to its occurrence in the environment are its formation as a product of the photochemical degradation of other atmospheric pollutants and its release in emissions from a wide variety of combustion processes.

Environmental Fate. The environmental fate of acrolein in air is well studied (Atkinson 1985; Atkinson et al. 1987; Gardner et al. 1987; Grosjean 1990). Given that acrolein occurs in the atmosphere from both natural and anthropogenic sources (Eisler 1994; EPA 1998a, 1998b; Graedal et al. 1978; Guilarducci and Tjeerdema 1995; Hodgkin et al. 1982; Jonsson et al. 1985; Lipari et al. 1984; Liu et al. 1999a, 1999b; Maldotti et al. 1980; WHO 1991, 2001), it would be helpful to have estimates of the relative contributions of these sources to acrolein concentrations in air, especially the contribution of the photochemical production of acrolein. Data on the dissipation and degradation of acrolein in water are available (Bowmer and Higgins 1976; Bowmer et al. 1974; Callahan et al. 1976, 1979; Ghilarducci and Tjeerdema 1995; Jacobson and Smith 1990; Kissel et al. 1978; Nordone et al. 1996; Rathbun 1998; Smith

et al. 1995; Tabak et al. 1981). No data were located on the removal of acrolein from water through reactions with dissolved and suspended organic matter in water. Studies on this route of removal of acrolein from water would be useful for determining the lifetime of acrolein in waters with high organic content. Data are available describing the absorption of acrolein to soil (Irwin 1988; Lyman 1982; Swann et al. 1983). However, experimental data pertaining to the persistence of acrolein in soil and groundwater are lacking. Studies on volatilization from soil surfaces, anaerobic biodegradation in soil and simulated groundwater, and aerobic biodegradation in simulated groundwater would be useful in establishing the likelihood of exposure near hazardous waste disposal sites resulting from volatilization from soil surfaces or from groundwater contamination.

Bioavailability from Environmental Media. No studies were located regarding the bioavailability of acrolein from environmental media. Since acrolein has been detected in ambient air and in food and beverages (ppb levels), it is important to determine if acrolein can be absorbed by humans from environmental samples. However, the chemical structure of acrolein makes it a highly reactive molecule, which presumably is why its effects are, for the most part, restricted to the area of exposure (i.e., respiratory system for inhalation exposure or localized skin damage for dermal exposure). The limited information available regarding absorption parameters of acrolein in experimental animals indicates that acrolein is easily retained in the respiratory airways (Egle 1972; Morris et al. 1996, 2003) and is, therefore, likely to act as an irritant of the eyes and respiratory tract with negligible absorption into the body. Virtually no information is available regarding absorption by the gastrointestinal tract or skin; additional studies would be useful in establishing whether acrolein is absorbed through these sites or is retained.

Food Chain Bioaccumulation. Measured and estimated BCF values for acrolein indicate that this compound would not bioaccumulate significantly in fish (Bysshe 1982; Hansch and Leo 1985; Veith et al. 1980). No information was available on the bioaccumulation of acrolein in organisms at other trophic levels in aquatic environments. Monitoring for the accumulation of acrolein in organisms from several trophic levels would be useful in estimating the levels of acrolein to which humans are exposed through dietary intake.

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

Data are available regarding the detection of acrolein in the environment, most notably in ambient air (Altshuller and McPherson 1963; CARB 1991; Destaillants et al. 2002; EPA 1998c, 1999, 2004a; Highsmith and Zweidinger 1988; IARC 1995; Mohamed et al. 2002; Morello-Frosch et al. 2000; Renzitti and Bryan 1961; Rosenbaum et al. 1999; WHO 1991, 2002), and also in water (EPA 1988a; Grosjean and Wright 1983; Krill and Sonzogni 1986; Otson 1987; WHO 2002), soil, and sediment (Hauser and Bromberg 1982). Some data are available on acrolein concentrations in air, water, landfill leachate, soil, and sediment samples taken either onsite or offsite from NPL or Superfund sites (HazDat 2005; Sabel and Clark 1984). Additional information on exposure to acrolein in air in urban areas, rural areas, near hazardous waste disposal sites, as well as in water (specifically, drinking water supplied from groundwater down gradient from hazardous waste disposal sites and contaminated surface waters) and soil at waste disposal sites would be useful. Monitoring air and water over a 1-year period would provide some indication of seasonal variations.

Exposure Levels in Humans. Data for residential exposure to acrolein are limited to a probabilistic study that provided a 24-hour time-weighted estimate of acrolein concentrations in air and inhalation intake for Canadian residents (Environment Canada 2000) and to a study on exposure of nonsmokers in the United States to acrolein in ETS (Nazaroff and Singer 2004). The development of a program for monitoring environmental media would provide information for better estimations of acrolein exposure levels in humans. Data are not available for intake of acrolein through the diet. Market basket surveys or total diet studies similar to those conducted by the FDA are needed to provide data on typical levels of exposure via dietary intake given the presence of acrolein in a number of foods (Cantoni et al. 1969; EPA 1980, 1985; Feron et al. 1991; IARC 1985; Umano and Shibamoto 1987; WHO 2002). Monitoring studies of acrolein concentrations in air are available for a few occupations such as shipyard workers, welders, plastic manufacturers, food service employees, and firefighters (Ahrenholz and Egilman 1983; Apol 1982; Ghilarducci and Tjeerdema 1995; Gochfeld 1995; Henriks-Eckerman et al. 1990; IARC 1985; Lees 1995; Materna et al. 1992; Tharr and Singal 1986; Trietman et al. 1980; Vainiotalo and Matveinen 1993; Woskie et al. 1988). Given the high likelihood of occupational exposures to acrolein as a consequence of its emission from combustion sources and the variability in the frequency and amount of exposures to the compound in various occupational settings, additional monitoring data are needed to provide reliable estimates of average daily intake of acrolein in workers.

Exposures of Children. Data on the exposure of children to acrolein are very limited (Nazaroff and Singer 2004; WHO 2002). For children living in a residence where one or more individuals smokes some

form of tobacco product, long-term exposure to acrolein and other compounds in ETS are expected (Nazaroff and Singer 2004; WHO 1999). Lifetime exposures to acrolein in ETS have been estimated for individuals residing with one or more smokers (Nazaroff and Singer 2004); however, there are no data that specifically address the inhalation intake of acrolein from ETS in individuals below the age of 18. Information on acrolein concentrations in indoor air is limited for residences in the United States (CARB 1992; Highsmith and Zweidinger 1988; WHO 2002). More data are needed to adequately assess the exposures of children to acrolein generated from indoor combustion sources, especially tobacco products. Determination of the average daily intake of acrolein would be complicated by the variability in the frequency and amount of exposure to cigarette smoke and other acrolein sources. Therefore, exposure studies should be structured to assess the temporal variations in acrolein concentrations over a typical day and should also account for seasonal changes in air exchange within a residence (i.e., winter versus summer). For children who are not exposed to ETS in the home environment, it is expected that the largest exposure to acrolein will be through inhalation of ambient air, especially in urban areas, and through the diet. Therefore, studies that are tailored to assessing exposure of children to acrolein in ambient air would be useful given the tendency for children to spend more time outdoors than many adults. Also, market basket surveys or total diet studies similar to those conducted by the FDA would be useful for providing data on typical levels of exposure via dietary intake for children.

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

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

6.8.2 Ongoing Studies

The EPA is developing the methods, data, and models of exposure that will provide the scientific basis for EPA to move to a risk-based program that will enhance the National-Scale Air Toxics Assessment (NATA) program. No other pertinent ongoing studies were identified.

7. ANALYTICAL METHODS

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

Data regarding the analytical methods used in the determination of acrolein in biological samples are limited. Boor and Ansari (1986) developed a method capable of detecting nanogram (ng) quantities of acrolein in biological samples. In this method, a derivatizing agent, 2,4-dinitrophenylhydrazine (DNP), is incubated with liver or kidney homogenate for a short period of time. The acrolein-DNP adduct is then extracted from the sample with chloroform. Analysis for acrolein is accomplished by elution on a reverse phase column using high performance liquid chromatography (HPLC), and detection of the adduct by ultraviolet (UV) absorbency. Interferences due to the coincidental elution of DNP adducts of ketones or aldehydes other than acrolein are not ruled out by this method of analysis.

In earlier attempts to quantify acrolein in biological media, Kissel (1978) urged caution when using derivatization methods for the measurement of acrolein levels in biological media based upon data for analysis for acrolein in aqueous solutions (Kissel et al. 1978). Methods that utilized derivatives (DNP and 7-hydroxyquinoline) combined with colorimetric or fluorimetric detection were not specific for acrolein and consistently did not correlate with those obtained from bioassays. However, more recent studies have made better utilization of gas chromatography (GC) and HPLC techniques to improve the resolution of acrolein and acrolein derivatives from other interfering species (Al-Rawithi et al. 1993; Paci et al. 2000; Sakuragawa et al. 1999). These assays, in addition to other assays for quantifying acrolein in biological media, are summarized in Table 7-1.

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent Recovery	Reference
Urine	Urine is heated to 80 °C, head-space vapors sampled, and injected directly into GC	GC-MS	1–5 nM (0.056–0.28 µg/L)	7–87.9% (100 nM)	Sakura et al. 1998
Urine	Urine is reacted with derivatizing reagent (*m*-aminophenol/ hydroxylamine/ferrous sulfate) and heated to 100 °C for 15 minutes.	HPLC-FD[b]	<1 µg/L	99–104.1%	Al-Rawithi et al. 1993
Urine	Urine is centrifuged, lypohilized, and reconstituted in water. The acrolein metabolite, 3-hydroxyl-propyl-L-cysteine, is directly quantified.	HPLC-UV	1.25 µg/mL (1.25 mg/L)	No data	Sanduja et al. 1988
Urine	The acrolein metabolite, 3-hydroxypropylmercapturic acid, in urine is hydrolyzed to 3-hydr-oxylpropyl-L-cysteine in 2N HCl	Amino acid analyzer	No data	No data	Alarcon 1976
Plasma	Plasma is reacted with Luminarin 3[a] in 0.1 M sulfuric acid, extracted with methylene chloride, dried, reconstituted in acetonitrile	HPLC-FD[b]	5.6 ng/mL (5.6 µg/L)	78–82%	Paci et al. 2000
Tissue	Homogenized tissued mixed with 2,4-DNP stock solution, extract acrolein-DNP derivative with chloroform	HPLC-UV[b]	<0.2 ng (in extract re-constituted in 0.5 mL methanol)	4.6–43.8% (8 mg acrolein)	Boor and Ansari 1986

[a]Derivatizing agent
[b]Derivative analyzed

2,4-DNP = 2,4-dinitrophenylhydrazine; FD = fluorescence detection; GC = gas chromatography; HPLC = high performance liquid chromatography; MS = mass spectrometry; UV = ultraviolet

A method for the direct detection of acrolein in urine was developed by Sakura et al. (1998). In this method, a small volume of urine (0.5 mL) is heated to 80 °C, driving the dissolved acrolein into the headspace above the liquid. The headspace vapors are analyzed using GC-mass spectrometry (MS), which provides a detection sensitivity of between 1 and 5 nM (0.056 and 0.28 µg/L) acrolein in urine. The variability is due to differences in the ability to drive acrolein from various urine samples during the heating phase of the method.

Biomarkers of acrolein exposure have been studied based either on acrolein metabolites in urine or the formation of protein-acrolein adducts. Alarcon (1976) developed a method for quantifying 3-hydroxypropylmercapturic acid (MCA), a known metabolite of acrolein, in urine. This method involves acidification of the urine to convert MCA to S-(3-hydroxypropyl)-L-cysteine. The amount of S-(3-hydroxypropyl)-L-cysteine can then be quantitated using an automated amino acid analyzer. Sanduja et al. (1989) directly measured S-(3-hydroxypropyl)-L-cysteine in urine at a sensitivity of 1.25 µg/mL using HPLC with UV detection (210 nm). Li et al. (2004) developed an enzyme-linked immunosorbent assay (ELISA) for detecting acrolein-protein adducts (APA) in albumin obtained from blood. The APA levels in plasma were found to increase by 32 and 58% in rates exposed to one or seven doses of 9.2 mg/kg/day acrolein, respectively. However, more work is necessary to correlate APA levels in plasma and acrolein exposures. Decreased activity of the enzyme, glucose-6-phosphate dehydrogenase (G6PD), has been found to occur when the purified form of the enzyme is exposed to 0.2–1.0 mM acrolein (Trieff et al. 1993). Studies have yet to be conducted to determine whether dose-dependent changes in G6DH activity are obtained *in vivo* as a function of exposures to acrolein.

7.2 ENVIRONMENTAL SAMPLES

The detection and quantification of acrolein in air is accomplished mainly through the formation of acrolein derivatives (Nishikawa and Sakai 1995). In the NIOSH method 2501 (NIOSH 1994), a known volume of air is pumped through a tube containing a support coated with the derivatizing agent 2-(hydroxymethyl)piperidine. The derivative is eluted from the tube with toluene, and analyzed by GC using a nitrogen specific detector (NSD). Variations of this procedure have also been reported. Rietz (1985) used DNP as a derivatizing agent on the adsorbent tube, and made a final analysis using HPLC coupled to a UV detector. Similarly, EPA method 8315A uses HPLC with UV detection to quantify the DNP derivative of acrolein that is obtained from the reaction of acrolein in air with 2,4-DNP coated on a silica matrix as air is pumped through a collection tube described in EPA method 100 (EPA 1996). The

DNP derivative is extracted with acetonitrile and analyzed using a C_{18} column and a detection wavelength of 360 nm.

Another method for quantifying acrolein in air involves the trapping of acrolein by bubbling air through an aliquot of ethanol, adding methoxylamine hydrochloride to form a derivative, and then brominating the resulting adduct to allow increased detector sensitivity. Quantitation is achieved by GC using an electron capture detector (ECD) (Nishikawa et al. 1986). A summary of these techniques, along with methods for other environmental samples, are presented in Table 7-2. Interferences due to coincidental elution of derivatives of the compounds can be a potential problem of these techniques depending on the resolving power of the chromatographic technique.

Derivatization methods for the measurement of acrolein levels in environmental media should be used with caution based upon data for analysis for acrolein in aqueous solutions (Kissel et al. 1978). In a comparison of chemical analytical methods to bioassays, results obtained using methods utilizing derivatives (DNP and 7-hydroxyquinoline) combined with colorimetric or fluorimetric detection were not specific for acrolein and consistently did not correlate with those obtained from bioassays. Certain direct methods of detection (nuclear magnetic resonance [NMR]), fluorescence, and differential pulse polarography) gave the best correlation to the bioassay results (see Table 7-2).

The analysis of acrolein in wastewater can be performed using EPA method 603 (EPA 1984). In closely related techniques, an aliquot of water is subjected to a purge and trap protocol, and the sample is thermally desorbed onto a GC for analysis and quantitation. Coincidental elution of compounds with acrolein may lead to interferences in this method.

Ogawa and Fritz (1985) developed a method for the identification of acrolein in water. A known volume of water is passed over a column of zeolite that traps the acrolein. The column is then eluted with acetonitrile, and derivatization using DNP follows. By following this procedure, a sample that can be analyzed by HPLC is obtained. Similar approaches were used by Koostra and Herbold (1995) and Sakuragawa et al. (1999), but in their methods, DNP was coated on to a C_{18} matrix within a solid phase extraction (SPE) cartridge. The use of mass spectrometric techniques by Sakuragawa et al. (1999) to quantify acrolein-DNP derivatives provided for better detection sensitivities than the UV detection method used by Koostra and Herbold. Other derivatizing agents that have been used successfully for the

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air[a]	Collection on tube with 2-(hydroxylmethyl)piperidine[b] coated on XAD-2 resin, desorbed by toluene extraction	GC-NSD[c] (NIOSH 2501)	2 µg	No data	NIOSH 1994
Air	Collection on tube containing silica gel coated with 2,4-dinitro-phenylhydrazine, tube backflushed with acetonitrile	HPLC-UV (EPA 100/ 8315A)	0.03 ppb (500 L sample volume)	No data	EPA 1996
Water	Direct analysis using detector wavelength of 195 nm	HPLC-UV (EPA 8316)	30 µg/L	No data	EPA 1994
Waste water[d]	Purge at 85 °C and trap onto methyl silicone/2,6-diphenylene oxide adsorbent, thermal desorption	GC-FID (EPA 603)	0.7 µg/L	104% (5µg/L, RW); 80% (5µg/L, POTW[e]); 2% (5µg/L, IW[f]);	EPA 1984
Waste water	Addition of isotopically-labeled standards, purge at 20–25 °C and trap onto methyl silicone/2,6-di-phenylene oxide adsorbent, thermal desorption	GC-MS (EPA 1624)	50 µg/L	No data	EPA 2001a
Air	Trap in ethanol solution, add methoxylaminehydrochloride[b], brominate	GC-ECD[c]	<4 ppb	81–96%	Nishikawa et al. 1986
	Trap on XAD-2 resin coated with 2-(hydroxymethyl)piperidine[b], desorb with toluene	GC-NSD[c]	NS	NS	Kennedy et al. 1984
	Trap on XAD-2 resin coated with 2,4-DNP[b], elute adduct with acetonitrile	HPLC-UV[c]	0.01 mg/m^3	No data	Rietz 1985
	Sampled air passed through ozone scrubber then through SPE cartridge where analytes are trapped on a C_{18} matrix coated with 2,4-DNP, elute adduct with acetontrile and dilute with water	HPLC-UV[c]	50–150 ng/m^3	>90%	Koostra and Herbold 1995
	Trap on C_{18} SPE coated with 2,4-DNP, extract with acetronitrile	LC-MS	0.44 ppb	100%	Sakuragawa et al. 1999

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Trap on Zeolite ZSM-5 column, elute with acetonitrile, derivatize with 2,4-DNP	HPLC-UV[c]	<10 µg	98%	Ogawa and Fritz 1985
	Nondirect measurement of aldehyde signal compared to signal for a calibrated sealed external TMS standard	NMR	5,000 ppm	NS	Kissel et al. 1978
	Dilution of sample with deionized water	Fluorescence spectrometer	>20 ppm	NS	Kissel et al. 1978
	Dilution of sample with deionized water, addition of phospate buffer and EDTA	Differential pulse polaro-graphy	>30 ppb	NS	Kissel et al. 1978
Personal Air	Trap on carbon coated with hydroquinone, desorb with 1,2-dichloroethane	GC	0.02 ppb	>75%	Hurley and Ketcham 1978
Rain	Add to collected sample methoxyl-aminehydrochloride[b], brominate	GC-ECD[c]	0.4 ng/mL	90–101%	Nishikawa et al. 1987b
Fats and natural oils	Fat or oil is emulsified in distilled water or 10 mM $HClO_4$, aqueous phase separated, then filtered and injected into column	HPLC-ED	0.15 µM	49–116%	Casella and Contursi 2004

[a]NIOSH method 2501 is the preferred method for quantitative analysis; method 2539 can be used to screen samples for acrolein.
[b]Derivatizing agent
[c]Derivative analyzed
[d]EPA method 603 is the preferred method for quantitative analysis; method 624 can be used to screen samples for acrolein.
[e]POTW = prechlorination secondary effluent from a municipal sewage treatment plant
[f]IW = industrial waste water containing an unidentified acrolein reactant

2,4-DNP = 2,4-dinitrophenylhydrazine; ECD = electron capture detector; ED = electrochemical detector; EDTA = ethylenediaminetetraacetic acid; FID = flame ionization detector; GC = gas chromatography; HPLC = high performance liquid chromatography; LC = liquid chromatography; MS = mass spectrometry; NMR = nuclear magnetic resonance; NS = not specified; NSD = nitrogen specific detector; POTW = publicly owned treatment works; RW = reagent water; SPE = solid phase extraction; TMS = tetramethylsilane; UV = ultraviolet

monitoring of acrolein in the environment include dimedon, phenylhydrazone, 4-hexylresorcinol, and 3-methyl-2-benzothiazolone (Altshuller and McPherson 1963; Peltonen et al. 1984).

Direct detection of acrolein in water is obtained using EPA method 8316 (EPA 1994). The water sample is injected on to a C_{18} HPLC column and then quantified by UV at a wavelength of 195 nm.

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 acrolein 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 acrolein.

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.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Methods have been identified that measure the concentrations of acrolein in blood, tissues, and urine (Al-Rawithi et al. 1993; Boor and Ansari 1986; Paci et al. 2000; Sakura et al. 1998). The methods used for the analysis of acrolein, however, can be susceptible to interferences.

Several studies have been identified that explore the use of specific biomarkers that can be associated quantitatively with exposure of acrolein. There are methods that can detect 3-hydroxypropylmercapturic acid, which is a metabolite of acrolein, in urine (Alarcon 1976; Sanduja et al. 1989). Changes in the activity of the enzyme, glucose-6-phosphate dehydrogenase, and levels in acrolein adducts of albumin in

blood as a function of exposure to acrolein have been studied (Li et al. 2004; Trieff et al. 1993), but further work is necessary to correlate exposures of acrolein with changes in the biomarkers *in vivo*.

Effect. There are no biomarkers that have been associated quantitatively with an acrolein-induced effect in humans. Indentification and use of such biomarkers would be useful for establishing a more reliable assessment of the relationship between acrolein intake and acrolein-induced effects in humans than would be provided from monitoring data of acrolein concentrations in air, drinking water, or food.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Suitable methods are available for the determination of acrolein in air, which mainly involve the formation of acrolein derivatives (Altshuller and McPherson 1963; Nishikawa and Sakai 1994; Peltonen et al. 1984) that are quantified using GC (Kennedy et al. 1984; NIOSH 1994; Nishikawa et al. 1986) or HPLC techniques (EPA 1996; Koostra and Herbold 1995; Rietz 1985). Suitable methods are also available for analyzing acrolein in water that either directly quantify acrolein in water (EPA 1994; Kissel et al. 1978, 1994) or use an extraction step followed by either analysis of acrolein (EPA 1986) or acrolein derivatives (EPA 1984; Ogawa and Fritz 1985). Nevertheless, new methodologies for the determination of acrolein have been reported. An LC-MS based method (Sakuragawa et al. 1999) can offer increased sensitivity and greater ease of performance than is currently available for the direct analysis of acrolein in water (Rietz 1985). Standardized methods for analyzing acrolein in soil were not located. However, given the extent to which acrolein is expected to volatilize from soil based on its high vapor pressure (274 mm Hg at 25 °C) and the irreversible binding of acrolein in soil, the lifetime of acrolein in soil may be too short for concern from the standpoint of being a source of human exposure to acrolein. Therefore, development of analytical methods for measuring acrolein in soil are not expected to provide data that would be useful in assessing human exposures to acrolein.

7.3.2 Ongoing Studies

The EPA is conducting a study on human exposure to air toxics, which includes optimizing the PAKS method for measuring airborne acrolein. At the University of California at Davis, Dr. M.J. Charles is developing an air sampling method that uses a Cofer scrubber for measuring acrolein in ambient air. Also at the University of California at Davis, Dr. Shibamoto is measuring the concentrations of acrolein in a variety of cooked foods and in beverages. Dr. Iype at the Biological Research Facility in Ijamsville, Maryland, is developing an antibody-mediated detection system for assessing human exposure to acrolein that is based on the quantification of acrolein-DNA adducts in white blood cells. No other ongoing

studies concerning the determination of acrolein in environmental media or biological materials were identified.

8. REGULATIONS AND ADVISORIES

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

ATSDR derived an acute-duration inhalation MRL of 0.003 ppm using a LOAEL of 0.3 ppm for nasal and throat irritation and decreased respiratory rate in volunteers exposed for 60 minutes (Weber-Tschopp et al. 1977). The LOAEL of 0.3 ppm was divided by a factor of 100 (10 for using a LOAEL and 10 for human variability).

ATSDR derived an intermediate duration inhalation MRL of 0.00004 ppm using a LOAEL of 0.4 ppm for nasal epithelial metaplasia in rats in a 13-week study (Feron et al. 1978). The MRL was calculated by dividing the human equivalent LOAEL (0.012 ppm) by an uncertainty factor of 300 (10 for using a LOAEL, 3 for extrapolation from animals to humans using dosimetric adjustments, and 10 for human variability).

ATSDR derived an intermediate-duration oral MRL of 0.008 mg/kg/day based on a NOAEL of 0.75 mg/kg/day for forestomach squamous epithelial hyperplasia in rats in a 13-week gavage study (NTP 1995) and an uncertainty factor of 100 (10 for species extrapolation and 10 for human variability).

EPA (IRIS 2005) has derived an inhalation reference concentration (RfC) for acrolein of $2x10^{-5}$ mg/m^3 based on a LOAEL of 0.9 mg/m^3 (0.4 ppm) for nasal lesions in male and female rats exposed to acrolein 6 hours/day, 5 days/week for 13 weeks (Freon et al. 1978) and an uncertainty factor of 1,000 (3 for use of a minimal LOAEL, 3 for interspecies extrapolation using dosimetric adjustments, 10 for extrapolation from subchronic to chronic duration, and 10 to account for human variability and sensitive subpopulations).

EPA (IRIS 2005) has derived an oral reference dose (RfD) for acrolein of $5x10^{-4}$ mg/kg/day based on a NOAEL of 0.05 mg/kg/day for decreased survival in male and female rats treated by oral gavage for 2 years (Parent et al. 1992a) and an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for intraspecies variability).

Table 8-1. Regulations and Guidelines Applicable to Acrolein

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 3[a]	IARC 2004
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines	No data	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (ceiling limit)[b]	0.10 ppm	ACGIH 2004
EPA	AEGL-1[c]		EPA 2005a
	10, 30, 60 minutes, 4 and 8 hours	0.03 ppm	
	AEGL-2[c]		
	10 minutes	0.44 ppm	
	30 minutes	0.18 ppm	
	60 minutes, 4 and 8 hours	0.10 ppm	
	AEGL-3[c]		
	10 minutes	6.2 ppm	
	30 minutes	2.5 ppm	
	60 minutes	1.4 ppm	
	4 hours	0.48 ppm	
	8 hours	0.27 ppm	
	Hazardous air pollutant	Yes	EPA 2004b 42 USC 7412
	Regulated toxic substances and threshold quantities for accidental release prevention	5,000 pounds	EPA 2005d 40 CFR 68.130
	Toxic end points for accidental release prevention	1.1×10^{-3} mg/L	EPA 2005i 40 CFR 68, Appendix A
NIOSH	REL (10-hour TWA)	0.1 ppm	NIOSH 2005
	STEL	0.3 ppm	
	IDLH	2.0 ppm	
OSHA	PEL (8-hour TWA) for general industry	0.1 ppm	OSHA 2005a 29 CFR 1910.1000
	PEL (8-hour TWA) for construction industry	0.1 ppm	OSHA 2005b 29 CFR 1926.55
	PEL (8-hour TWA) for shipyard industry	0.1 ppm	OSHA 2005d 29 CFR 1910.1000
	Highly hazardous chemical and threshold quantity[d]	150 pounds	OSHA 2005c 29 CFR 1910.119
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311 of the Clean Water Act	Yes	EPA 2005b 40 CFR 116.4
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	1 pound	EPA 2005e 40 CFR 117.3
	Water quality criteria for human health consumption of:		EPA 2002
	Water + organism	190 µg/L	
	Organism only	290 µg/L	

Table 8-1. Regulations and Guidelines Applicable to Acrolein

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
c. Food		No data	
d. Other			
ACGIH	Carcinogenicity classification	A4[e]	ACGIH 2004
EPA	Carcinogenicity classification	Cannot be determined[f]	IRIS 2005
	RfC	$2x10^{-5}$ mg/m^3	
	RfD	$5x10^{-4}$ mg/kg/day	
	Pesticide classified for restricted use[g]	Yes	EPA 2005c 40 CFR 152.175
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance[h]		EPA 2005f 40 CFR 302.4
	Reportable quantity	1 pound	
	RCRA waste number	P003	
	Effective date of toxic chemical release reporting	01/01/87	EPA 2005h 40 CFR 372.65
	Extremely hazardous substances		EPA 2005g
	Reportable quantity	1 pound	40 CFR 355,
	Threshold planning quantities	500 pounds	Appendix A
NTP	Carcinogenicity classification	No data	NTP 2005

[a]Group 3: not classifiable as to carcinogenicity to humans.
[b]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.
[c]AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.
[d]Highly hazardous chemical: presents a potential for a catastrophic event at or above the threshold quantity.
[e]A4: not classifiable as a human carcinogen.
[f]Potential carcinogenicity cannot be determined because the existing "data are inadequate for an assessment of human carcinogenic potential for either the oral or inhalation route of exposure".
[g]Pesticide classified for restricted use because of the inhalation hazard to humans and the residue effects on avian species and aquatic organisms.
[h]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) and 307(a) of the Clean Water Act, Section 112 of the Clean Air Act, and Section 3001 of RCRA.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline level; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; 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; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; 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-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without 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.

10. GLOSSARY

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 of a substance that should not be exceeded, even instantaneously.

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

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 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)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

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 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 chemical.

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) allowable exposure level in workplace air averaged over an 8-hour 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.

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 air/blood 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 chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

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 chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, 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)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

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 most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

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

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 chemical 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 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 chemical-induced end point 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 Environmental Medicine, 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 Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Acrolein
CAS Number: 107-02-8
Date: July 2005
Profile Status: Final Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 4
Species: Human

Minimal Risk Level: 0.003 [ ] mg/kg/day [X] ppm

Reference: Weber-Tschopp A, Fischer T, Gierer R, et al. 1977. [Experimental irritating effects of acrolein on man.] Int Arch Occup Environ Health 40:117-130. (German)

Experimental design: Forty-six volunteers (21 men, 25 women) were placed into an exposure chamber in groups of 3 and exposed to 0.3 ppm acrolein for 60 minutes. At 5-minute intervals during exposure, participants used a questionnaire to score the level of eye, nose, and throat irritation as 1 (not at all), 2 (a little), 3 (medium), and 4 (strong). In each exposure group, blink rate was observed in two of the three participants, while breathing rate was measured in the third participant. There was no control group or statistical analysis.

In another experiment reported in Weber-Tschopp et al. (1977), volunteers were exposed to a gradually increasing concentration of acrolein for 40 minutes. As acrolein levels rose from 0 to 0.6 ppm over a 35-minute period, participants subjectively scored irritancy at 5-minute intervals as described previously. At the end of 35 minutes, volunteers were exposed for 5 additional minutes at 0.6 ppm. The LOAEL for nose irritation of 0.26 ppm had an average score between 1 and 2 and was statistically significant relative to controls. A NOAEL of 0.17 ppm was identified, which was not statistically different from controls. However, the changing concentrations of acrolein make it difficult to fix the duration or level of exposure that was actually responsible for the onset of noticeable irritation.

Effects noted in study and corresponding doses: Intensity of nose irritation reached a maximum mean score of 2 (a little) at approximately 40 minutes into the exposure, with no change through the remaining 20 minutes. Intensity of throat irritation reached a maximum mean score of between 1 (not at all) and 2 (a little) at approximately 40 minutes into the exposure, with no increase in intensity scores for the remaining 20 minutes. Intensity of nose and throat irritation was scored significantly higher than pre-exposure values beginning at 10 minutes. A 20% decrease in respiratory rate was also observed, compared to pre-exposure values. Controls from the dynamic concentration experiment reported mean scores that were very close to 1 (not at all) for the entire 40-minute test.

Dose and end point used for MRL derivation: LOAEL of 0.3 ppm; decrease in respiratory rate, nose and throat irritation.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

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

Other additional studies or pertinent information which lend support to this MRL: Cassee et al. (1996) exposed 5–6 rats to acrolein vapor levels of 0.25, 0.67, and 1.4 ppm, 6 hours/day for 3 consecutive days. The most sensitive response was mild necrosis, dysplasia, and desquamation of nasal epithelium in rats exposed to 0.25 ppm. Statistically significant cellular proliferation was also observed at 0.25 ppm. Aranyi et al. (1986) reported reduced bactericidal activity of the respiratory tract in mice following acute acrolein inhalation exposures. Significantly lower alveolar macrophagic clearance of a 3-hour *Klebsiella. pneumoniae* infection was observed following a 5-day exposure to 0.1 ppm acrolein in mice. This exposure represents the lowest LOAEL identified for inhalation exposure to acrolein. Treated mice removed 77% of bacteria from their lungs, while controls removed 84%. Though statistically significant, it is not clear what, if any, significance for pathogenicity this difference has on secondary bacterial infections following acrolein exposures. No difference was observed in rats for this same exposure/infection protocol (Sherwood et al. 1986). The Cassee et al. (1996) study provides a clinically objective measure of nasal irritation in rats; however, the derived LOAEL (0.25 ppm) was very similar to the human LOAEL (0.3 ppm) from Weber-Tschopp et al. (1977). This being the case, the human-derived data are preferable for the basis for the MRL, eliminating the introduction of uncertainty from inter-species extrapolation.

Agency Contacts (Chemical Managers): Nickolette Roney, Jessilynn Taylor, and Annette Ashizawa

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Acrolein
CAS Number: 107-02-8
Date: July 2005
Profile Status: Final Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 32
Species: Rat

Minimal Risk Level: 0.00004 [ ] mg/kg/day [X] ppm

Reference: Feron VJ, Kruysse A, Til HP, et al. 1978. Repeated exposure to acrolein vapour: Subacute studies in hamsters, rats and rabbits. Toxicology 9:47-58.

Experimental design: Groups of 12 rats, 20 hamsters, and 4 rabbits were exposed to 0, 0.4, 1.4, and 4.9 ppm acrolein, 6 hours/day, 5 days/week for 13 weeks. General clinical observations were made daily. Body weights and food consumption was recorded weekly. Hematological and serum chemistry measurements were taken at week 12. After euthanasia of animals, organs were removed, weighed, and fixed for histological analysis.

Effects noted in study and corresponding doses: Nasal metaplasia occurred in rats at 0.4 ppm. At 1.4 ppm, rats exhibited squamous epithelia metaplasia, rabbits exhibited decreases in body weight gains, and hamsters exhibited nasal inflammation. At 4.9 ppm, all species exhibited necrotizing rhinitis. Rats exhibited increased heart and kidney weight, tracheal and bronchiolar metaplasia, and lung edema and hemorrhage, and death. Hamsters exhibited increased kidney and heart weight.

Dose and end point used for MRL derivation: LOAEL of 0.4 ppm; nasal epithelial metaplasia in rats. In Feron et al. (1978), the authors did not report incidence data for inhalation effects. Therefore, benchmark dose analysis could not be performed.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans using dosimetric adjustments
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Duration adjusted LOAEL ($LOAEL_{ADJ}$) = 0.4 ppm x 6/24 hours x 5/7 days = 0.071 ppm

Regional gas dose ratio for the extrathoracic region ($RGDR_{ER}$) for a category 1 gas =

$$RGDR_{ET} = \frac{\left[\frac{\dot{V}_E}{SA_{ET}}\right]_R}{\left[\frac{\dot{V}_E}{SA_{ET}}\right]_H} = 0.17$$

Where:

V_e is the minute volume and SA_{ET} is the surface area of the extrathoracic (ET) region of the respiratory tract.

Minute volume (V_e)

Human: 13.8 L/minute (EPA 1994)
Rat: 0.16 L/minute; calculated using the following EPA (1994), reference erroneously uses common logarithm in calculations) equation:

$$\ln(V_e) = b_0 + b_1 \ln(BW)$$

For rats, b_0 equals -0.578 and b_1 equals 0.821 and a body weight of 0.217 kg (EPA 1988c).

EPA (1994b) rat and human respiratory surface area reference values:

Extrathoracic 15.0 cm^2 (rat) 200 cm^2 (human)

$LOAEL_{HEC} = LOAEL_{ADJ}$ x RGDR = 0.071 ppm x 0.17 = 0.012 ppm

Other additional studies or pertinent information which lend support to this MRL: In Feron et al. (1978), the rat appeared to be the most sensitive species, exhibiting more severe histological changes across the respiratory tract than the other species. In other studies, exposures to acrolein concentrations between 0.4 and 5.0 ppm for up to 180 days caused a continuum of histological alterations, inflammation, and severe tissue destruction across the entire respiratory tract of rats, rabbits, guinea pigs, and monkeys. Several similar effects were observed throughout the respiratory tract and across species in the 1–2-ppm exposure level, including nasal epithelial inflammation in hamsters (Feron et al. 1978), tracheal hyperplasia in monkeys (Lyon et al. 1970), bronchiolar inflammation in rats (Kutzman et al. 1985), and lung hyperplasia and inflammation in rats (Costa et al. 1986; Lyon et al. 1970). Effects in the deeper respiratory tract became more severe at the 3–5-ppm exposure levels. Effects included tracheal epithelial metaplasia in hamsters (Feron et al. 1978), epithelial dysplasia in rats (Leach et al. 1987), squamous lung epithelial metaplasia in rats (Kutzman et al. 1985), tracheal metaplasia and bronchial necrosis in rats (Feron et al. 1978; Kutzman et al. 1985), pulmonary edema in rats (Costa et al. 1986), and lung hemorrhage in monkeys (Lyon et al. 1970). The Feron et al. (1978) study was chosen as the critical study since it provided the lowest LOAEL of 0.4 ppm for nasal epithelial metaplasia, the most sensitive effect.

Agency Contacts (Chemical Managers): Nickolette Roney, Jessilynn Taylor, and Annette Ashizawa

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Acrolein
CAS Number: 107-02-8
Date: July 2005
Profile Status: Final Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 14
Species: Rat

Minimal Risk Level: 0.008 [X] mg/kg/day [ ] ppm

Reference: NTP. 1995. 13-Week gavage toxicity studies of allyl acetate, allyl alcohol, and acrolein in Fisher 344 rats and B6C3F1 mice. National Toxicology Program.

Experimental design: Groups of 10 rats/sex/dose were administered 0.75, 1.25, 2.5, 5, and 10 mg/kg/day by gavage for 13 weeks, while groups of 10 mice/sex/dose were given 1.25, 2.5, 5, 10, and 20 mg/kg for the same duration. Dose volumes were 5 mL/kg for rats and 10 mL/kg for mice.

Effects noted in study and corresponding doses: Common high-dose effects were observed for both species, including hemorrhage and necrosis, and forestomach and glandular stomach lesions. Rats receiving 10 mg/kg/day exhibited abnormal breathing, nasal discharge, and death. The lowest LOAEL observed was 1.25 mg/kg/day for forestomach squamous epithelial hyperplasia in female rats, with an associated NOAEL of 0.75 mg/kg/day. In male rats, the lowest LOAEL observed was 2.5 mg/kg/day with an associated NOAEL of 1.25 mg/kg/day. Mice exhibited no clinical signs of toxicity. Glandular stomach lesions appeared in the 10 and 20 mg/kg/day males and in the 20 mg/kg/day female mice. Liver weights were significantly increased in male mice given 10 mg/kg/day. In male mice, the lowest LOAEL observed was 1.25 mg/kg/day with no associated NOAEL (since 1.25 mg/kg/day was the lowest dose tested in mice).

Dose and end point used for MRL derivation: NOAEL of 0.75 mg/kg/day; forestomach squamous epithelial hyperplasia in rats.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

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

Other additional studies or pertinent information which lend support to this MRL: Gastric ulceration was observed in rats given an acute gavage doses of 25 mg/kg (Sakata et al. 1989) and in rabbits given 4 mg/kg/day for 12 days (Parent et al. 1993). Gastric ulceration was also seen in rats given intermediate-

duration doses of 5.4 mg/kg/day for 115 days (King 1984). Vomiting was also observed in a chronic gavage study in which dogs were given 0.1 mg/kg/day (Parent et al. 1992b). Epithelial hyperplasia is a sensitive end point for nasal effects of acrolein inhalation as seen in rats receiving 1.4 ppm for 62 days (Costa et al. 1986) and in dogs exposed to 3.7 ppm for 6 weeks (Lyon et al. 1970). Forestomach squamous epithelial hyperplasia represented the lowest identified LOAEL in a well-designed study.

The NTP (1995) study was not available; however, the study data are available on the NTP website.

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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 chemical 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 are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (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 harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system,

which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The 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.

SAMPLE

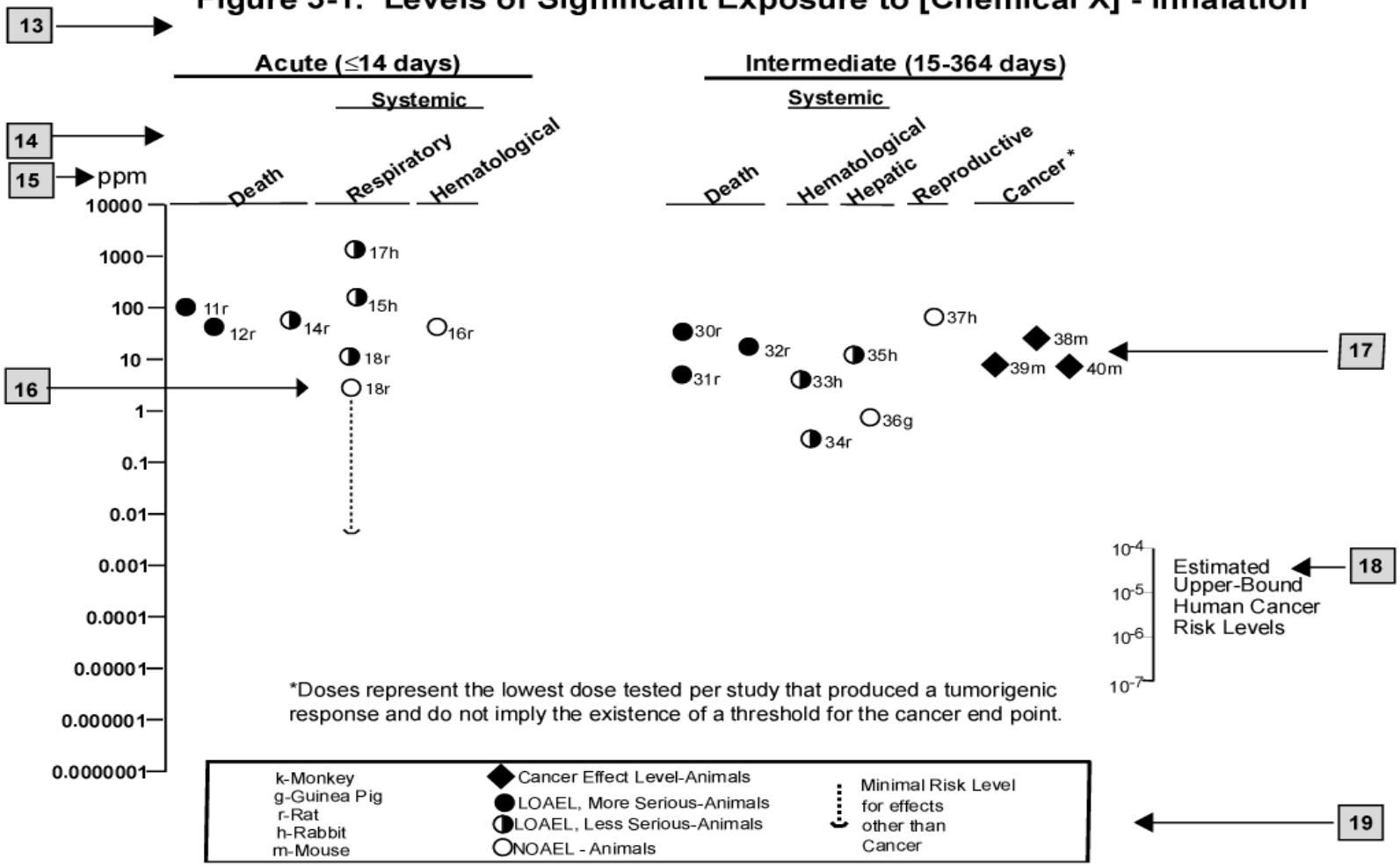
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	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	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	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



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	benchmark dose
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
CL	ceiling limit value
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/IMCO	Department of Transportation/United Nations/North America/International 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	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
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
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
RfC	reference concentration
RfD	reference dose
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
SGPT	serum glutamic pyruvic transaminase
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
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

APPENDIX D. INDEX