TOXICOLOGICAL PROFILE FOR AMMONIA

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

September 2004

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Ammonia, Draft for Public Comment, was released in September 2002. 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/Toxicology Information 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:

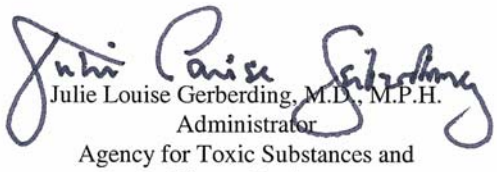
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(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.

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 was 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.
Administrator
Agency for Toxic Substances and
Disease Registry

*Legislative Background

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 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); 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); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Nickolette Roney, MPH
ATSDR, Division of Toxicology, Atlanta, GA

Fernando Llados, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

Susan S. Little, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

David B. Knaebel, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

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.

PEER REVIEW

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

1. Dr. Finis Cavender, Private Consultant, Greer, South Carolina;

2. Dr. Jerold Last, Professor, Internal Medicine, University of California, Davis;

3. Dr. Frederick Oehme, Professor of Toxicology, Medicine/Physiology, Kansas State University; and

4. Dr. Martin Alexander, Professor, Department of Soil, Crop, and Atmospheric Sciences, Cornell University, New York.

These experts collectively have knowledge of ammonia's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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

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

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This public health statement tells you about ammonia and the effects of exposure.

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. Ammonia has been found in at least 137 of the 1,647 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 ammonia 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 ammonia, 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 AMMONIA?

Ammonia is a chemical that is made both by humans and by nature. It is made up of one part nitrogen (N) and three parts hydrogen (H_3). The amount of ammonia manufactured every year by humans is almost equal to the amount produced by nature every year. However, when ammonia is found at a level that may cause concern, it was likely produced either directly or indirectly by humans.

1. PUBLIC HEALTH STATEMENT

Ammonia is a colorless gas with a very sharp odor. Ammonia in this form is also known as ammonia gas or anhydrous ("without water") ammonia. Ammonia gas can also be compressed and becomes a liquid under pressure. The odor of ammonia is familiar to most people because ammonia is used in smelling salts, household cleaners, and window cleaning products. Ammonia easily dissolves in water. In this form, it is also known as liquid ammonia, aqueous ammonia, or ammonia solution. In water, most of the ammonia changes to the ionic form of ammonia, known as ammonium ions, which are represented by the formula NH_4^+ (an ion is an atom or a group of atoms that has acquired a net electric charge by gaining or losing one or more electrons). Ammonium ions are not gaseous and have no odor. Ammonia and ammonium ions can change back and forth in water. In wells, rivers, lakes, and wet soils, the ammonium form is the most common. Ammonia can also be combined with other substances to form ammonium compounds, including salts such as ammonium chloride, ammonium sulfate, ammonium nitrate, and others.

Ammonia is very important to plant, animal, and human life. It is found in water, soil, and air, and is a source of much needed nitrogen for plants and animals. Most of the ammonia in the environment comes from the natural breakdown of manure and dead plants and animals.

Eighty percent of all manufactured ammonia is used as fertilizer. A third of this is applied directly to soil as pure ammonia. The rest is used to make other fertilizers that contain ammonium compounds, usually ammonium salts. These fertilizers are used to provide nitrogen to plants. Ammonia is also used to manufacture synthetic fibers, plastics, and explosives. Many cleaning products also contain ammonia in the form of ammonium ions.

For detailed information on the chemical properties of ammonia, see Chapter 4. Details on the production and use of ammonia are in Chapter 5, and more information on the environmental fate of ammonia and sources of human exposure is in Chapter 6.

1.2 WHAT HAPPENS TO AMMONIA WHEN IT ENTERS THE ENVIRONMENT?

Since ammonia occurs naturally in the environment, we are regularly exposed to low levels of ammonia in air, soil, and water. Ammonia exists naturally in the air at levels between 1 and 5 parts in a billion parts of air (ppb). It is commonly found in rainwater. The ammonia levels in rivers and bays are usually less than 6 parts per million (ppm; 6 ppm=6,000 ppb). Soil typically contains about 1–5 ppm of ammonia. The levels of ammonia vary throughout the day, as well as from season to season. Generally, ammonia levels are highest in the summer and spring. Ammonia is essential for mammals and is necessary for making DNA, RNA, and proteins. It also plays a part in maintaining acid-base balance in tissues of mammals.

Ammonia does not last very long in the environment. Because it is recycled naturally, nature has many ways of incorporating and transforming ammonia. In soil or water, plants and microorganisms rapidly take up ammonia. After fertilizer containing ammonia is applied to soil, the amount of ammonia in that soil decreases to low levels in a few days. In the air, ammonia will last about 1 week.

Ammonia has been found in air, soil, and water samples at hazardous waste sites. In the air near hazardous waste sites, ammonia can be found as a gas. Ammonia can also be found dissolved in ponds or other bodies of water at a waste site. Ammonia can be found attached to soil particles at hazardous waste sites. The average concentration of ammonia reported at hazardous waste sites ranges from 1 to 1,000 ppm in soil samples and up to 16 ppm in water samples.

See Chapter 6 for more detailed information on the environmental fate of ammonia, ammonia levels in the environment, and exposure to ammonia.

1.3 HOW MIGHT I BE EXPOSED TO AMMONIA?

Ammonia is naturally produced and used by all mammals in their normal metabolism. Ammonia is produced within a person’s body each day. Most of this ammonia is produced by organs and tissues, but some is produced by bacteria living inside our intestines.

Ammonia is found naturally in the environment. You may be exposed to ammonia by breathing air, eating food, or drinking water that contains it, or through skin contact with ammonia or ammonium compounds. Exposure to ammonia in the environment is most likely to occur by breathing in ammonia that has been released into the air.

Ammonia has a very strong odor that is irritating and that you can smell when it is in the air at a level higher than 50 ppm. Therefore, you will probably smell ammonia before you are exposed to a concentration that may harm you. Levels of ammonia in air that cause serious effects in people are much higher than levels you would normally be exposed to at home or work. However, low levels of ammonia may harm some people with asthma and other sensitive individuals.

You can taste ammonia in water at levels of about 35 ppm. Lower levels than this occur naturally in food and water. Swallowing even small amounts of liquid ammonia in your household cleaner might cause burns in your mouth and throat. A few drops of liquid ammonia on the skin or in the eyes will cause burns and open sores if not washed away quickly. Exposure to larger amounts of liquid ammonia or ammonium ion in the eyes causes severe eye burns and can lead to blindness.

Outdoors, you may be exposed to high levels of ammonia gas in air from leaks and spills at production plants and storage facilities, and from pipelines, tank trucks, railcars, ships, and barges that transport ammonia. Higher levels of ammonia in air may occur when fertilizer with ammonia or ammonium compounds is applied to farm fields. After fertilizer is applied, the concentration of ammonia in soil can be more than 3,000 ppm; however, these levels decrease rapidly over a few days.

Indoors, you may be exposed to ammonia while using household products that contain ammonia. Some of these products are ammonia-cleaning solutions, window cleaners, floor waxes, and smelling salts.

Household and industrial cleaning solutions may contain ammonia, and use of these products at home or work may lead to exposure to ammonia. Both types of ammonia cleaning solutions are made by adding ammonia gas to water to form liquid ammonia. Household ammonia cleaners typically contain lower levels of ammonia (between 5 and 10%) compared to industrial cleaning solutions, which can contain higher levels of ammonia (up to 25%).

Farmers can be exposed to ammonia when they work with or apply fertilizers containing ammonia to fields. Farmers, cattle ranchers, and people who raise other types of livestock and/or poultry can be exposed to ammonia from decaying manure. Some manufacturing processes also use ammonia. Some older refrigeration units used ammonia as the refrigerant.

For more information on levels of exposure associated with effects, see Chapter 3.

1.4 HOW CAN AMMONIA ENTER AND LEAVE MY BODY?

Ammonia can enter your body if you breathe in ammonia gas or if you swallow water or food containing ammonium salts. If you spill a liquid containing ammonia on your skin, a small amount of ammonia might enter your body through your skin; however, more ammonia will probably enter as you breathe ammonia gas from the spilled ammonia. After you breathe in ammonia, you breathe most of it out again. The ammonia that is retained in the body is changed into ammonium compounds and carried throughout the body in seconds. If you swallow ammonia in food or water, it will get into your bloodstream and be carried throughout your body in seconds. Most of the ammonia that enters your body from food or water rapidly changes into other substances that will not harm you. The rest of this ammonia leaves your body in urine within a couple of days. For more information on how ammonia can enter and leave your body, see Chapter 3.

1.5 HOW CAN AMMONIA 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.

Ammonia is a corrosive substance and the main toxic effects are restricted to the sites of direct contact with ammonia (i.e., skin, eyes, respiratory tract, mouth, and digestive tract). For example, if you spilled a bottle of concentrated ammonia on the floor, you would smell a strong ammonia odor; you might cough, and your eyes might water because of irritation. If you were exposed to very high levels of ammonia, you would experience more harmful effects. For example, if you walked into a dense cloud of ammonia or if your skin comes in contact with concentrated ammonia, your skin, eyes, throat, or lungs may be severely burned. These burns might be serious enough to cause permanent blindness, lung disease, or death. Likewise, if you accidentally ate or drank concentrated ammonia, you might experience burns in your mouth, throat, and stomach. There is no evidence that ammonia causes cancer. Ammonia has not been classified for carcinogenic effects by EPA, Department of Health and Human Services (DHHS) (NTP), or the International Agency for Research on Cancer (IARC). Ammonia can also have beneficial effects, such as when it is used as a smelling salt. Certain ammonium salts have long been used in veterinary and human medicine. For more information on how ammonia can affect your health, see Chapter 3.

1.6 HOW CAN AMMONIA AFFECT CHILDREN?

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

Children are less likely than adults to be exposed to concentrated ammonia because most exposures to concentrated ammonia occur in occupational settings. Children can still be exposed in the same way as adults to ammonia gas from spills or leaks from ammonia tanks or pipelines, especially on farms where it is used as a fertilizer. Children can also be exposed to dilute ammonia solutions from household cleaners containing ammonia.

The effects of ammonia on children are likely to be the same as for adults. Ammonia is an irritant and the solution and gas can cause burns of the skin, eyes, mouth, and lungs. If a spill occurs, children may be exposed to ammonia for a longer time than adults because they may not leave the area as quickly.

There is no evidence that exposure to the levels of ammonia found in the environment causes birth defects or other developmental effects. It is not known whether ammonia can be transferred from a pregnant mother to a developing fetus through the placenta or from a nursing mother to her offspring through breast milk. One study in animals showed that exposure of mothers to very high levels of ammonia during pregnancy caused their newborn offspring to be smaller than normal, but this occurred at levels of ammonia that also affected the mothers.

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

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

You can reduce your risk of exposure to ammonia by carefully using household products and by avoiding areas where ammonia is used or produced. At home, you can reduce your risk of

exposure to ammonia by careful handling of any household products that contain ammonia. For example, some cleaning products contain ammonia; so when you use them, you should be sure that rooms are adequately ventilated during the time you are using them. Avoid ammonia-containing products in glass bottles since breakage could lead to a serious exposure. You should wear proper clothing and eye protection, because ammonia can cause skin burns and damage eyes if it is splashed on them. To lower the risk of your children being exposed to ammonia, you should tell them to stay out of the room when you are using it. While use of ammonia by a child is not recommended, any use by a child should be closely supervised by an adult.

You can also reduce your risk of exposure to ammonia by avoiding areas where it is being used. Ammonia is used to fertilize crops, so you can lower your exposure to ammonia by avoiding these areas when it is being applied. You can also lower your exposure to ammonia by avoiding places where it is produced. Ammonia is found in many animal wastes, and it may be present in high concentrations in the air in livestock buildings. You can lower your exposure to ammonia by avoiding these buildings, especially if large numbers of animals are inside.

If you are a worker who uses or applies ammonia for farming, you can reduce your exposure by using it according to the instructions and wearing proper clothing and protective gear. Be sure to follow all instructions and heed any warning statements.

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

There are tests that measure ammonia/ammonium ion in blood and urine; however, these tests would probably not tell you whether you have been exposed because ammonia is normally found in the body. If you were exposed to harmful amounts of ammonia, you would notice it immediately because of the strong, unpleasant, and irritating smell, the strong taste, and because of skin, eye, nose, or throat irritation. Exposure detection levels and methods for determining ammonia levels in biological materials are discussed in 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 ammonia include the following:

EPA regulates the ammonia content in waste water released by several industries. Any discharges or spills of ammonia of 100 pounds or more, or of ammonium salts of 1,000 or 5,000 pounds (depending upon the compound), must be reported to EPA.

Some restrictions have been placed on levels of ammonium salts allowable in processed foods. FDA states that the levels of ammonia and ammonium compounds normally found in food do not pose a health risk. Maximum allowable levels in processed foods are as follows: 0.04–3.2% ammonium bicarbonate in baked goods, grain, snack foods, and reconstituted vegetables; 2.0% ammonium carbonate in baked goods, gelatins, and puddings; 0.001% ammonium chloride in

baked goods and 0.8% in condiments and relishes; 0.6–0.8% ammonium hydroxide in baked goods, cheeses, gelatins, and puddings; 0.01% monobasic ammonium phosphate in baked goods; and 1.1% dibasic ammonium phosphate in baked goods, 0.003% in nonalcoholic beverages, and 0.012% in condiments and relishes.

OSHA has set an 8-hour exposure limit of 25 ppm and a short-term (15-minute) exposure limit of 35 ppm for ammonia in the workplace. NIOSH recommends that the level in workroom air be limited to 50 ppm for 5 minutes of exposure.

Further information on governmental recommendations can be found in Chapter 8.

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
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 AMMONIA IN THE UNITED STATES

Ammonia is a natural compound, as well as a manufactured compound. In nature, most ammonia probably comes from decomposing animal excreta, with the decay of organic materials from plants, dead animals, and the like also contributing significant amounts. It is also exhaled by animals. Production of fixed nitrogen (NH_3) by plants and microorganisms is estimated at 90 to 130 metric tons annually. Manufacture of ammonia within the United States was 9.5 million metric tons in 2001, which is down from 16.6 million metric tons in 1999. Commercially produced ammonia is used primarily as fertilizer, with plastics, synthetic fibers and resins, explosives, and other uses accounting for most of the remainder.

Ammonia is released to the atmosphere by natural processes such as the decay of organic matter and animal excreta, or by volcanic eruptions. It can also be released to the atmosphere by anthropogenic activities such as fertilizer use; spillage or leakage from storage or production facilities; or loss from waste water effluents. The average global ammonia concentration in the atmosphere ranges from 0.3 to 6 ppb, with concentrations sometimes higher in the vicinity of agricultural or industrial areas. For example, near industrial sources or manure heaps in Germany, ammonia concentrations ranged from 10.3 to 89 ppb. Concentrations may be orders of magnitude higher near some types of livestock areas, such as pigpens, where local atmospheric concentrations have been reported to be as high as 47 ppm.

Elevated concentrations of ammonia in water are usually due to effluent discharges from sewage treatment plants or industrial processes, or runoff from fertilized fields or livestock areas. Ammonia concentrations can therefore vary widely in aquatic environments, with concentrations being lower in bodies of water that are unimpacted by residential, industrial, or farming effluents, compared to those that are impacted (where concentrations can be orders of magnitude higher). In unimpacted waterways, ammonia concentrations have been reported to range from 8.5 to 43 ppb, whereas in impacted waterways, concentrations as high as 16 ppm have been reported.

Soils usually obtain additional ammonia from natural or synthetic fertilizer application, animal excreta, decaying organic matter, or natural fixation from the atmosphere. Soils have been reported to have background concentrations of ammonia ranging from 1 to 5 ppm. Immediately following application of

fertilizer or manure, however, ammonia concentrations can rise to 2–3,000 ppm, with levels dropping after 5 days to 2–850 ppm. These high ammonia concentrations are usually limited to the upper few centimeters of topsoil.

In the atmosphere, ammonia can react with acidic substances in the air to produce ammonium aerosols, which can be subject to dry or wet deposition. The best estimate of the half-life of atmospheric ammonia is a few days. In water, ammonia can volatilize to the atmosphere, be removed by microbial processes, or adsorb to sediment and suspended organic material. In soil, ammonia can volatilize to the atmosphere, adsorb to soil particles, undergo microbial transformation to nitrate or nitrite anions, or be taken up by plants.

For the general population, the most likely source of exposure to elevated levels of ammonia is from the use of household cleaners containing ammonia or ammonium salts. People who live near farms, who visit farms during the application of fertilizer, or who live near cattle feedlots, poultry confinement buildings, or other areas where animal populations are concentrated can also be exposed to ammonia. Local atmospheric concentrations in these agricultural settings have been reported to range from 280 to 88,000 ppb.

There is also the possibility for exposure to ammonia via water and food ingestion. If untreated surface water is ingested, the average uptake would be 0.36 mg/day (assuming an ammonia concentration in untreated water of 0.18 mg/L and a consumption rate of 2 L/day). For most sources of drinking water, however, adsorption, nitrification, and the conversion of ammonia to chloramines upon chlorination will result in negligible levels of ammonia in most drinking water supplies. Food ingestion can also lead to an exposure to ammonia, primarily due to the use of various ammonium salts as food stabilizers; the estimated exposure from these food additives is 18 mg/day.

Populations that live or work near a hazardous waste site that contains ammonia or ammonium salts could be exposed to above-average levels of ammonia in soil, water, or air in similar concentrations as those in agricultural settings. While these exposures may occur, the half-life of ammonia in nature is probably very short. Ammonia has been identified in at least 137 of 1,647 National Priority List (NPL) hazardous waste sites.

2.2 SUMMARY OF HEALTH EFFECTS

Ammonia is an essential mammalian metabolite for DNA, RNA, and protein synthesis and is necessary for maintaining acid-base balance. Ammonia is produced and used endogenously in all mammalian species. It has been estimated that up to 17 grams of ammonia are produced in humans daily. Of these 17 grams, approximately 4 grams are produced in the gut by intestinal bacteria, where it enters the portal circulation and is metabolized rapidly in the liver to urea. Ammonia is excreted primarily as urea and urinary ammonium compounds through the kidneys. Levels of ammonia in the blood from healthy humans range from 0.7 to 2 mg/L.

The most important injurious effects of exposure to excessive amounts of ammonia on humans are due to its irritative and corrosive properties. Exposures to ammonia gas cause chemical burns of the respiratory tract, skin, and eyes. Ammonia dissolves in the water present in skin, mucous membranes, and eyes and becomes ammonium hydroxide, which is a highly ionized weak base that causes necrosis of the tissues. Specifically, ammonium hydroxide causes saponification of cell membrane lipids resulting in cell disruption and death. Additionally, it extracts water from the cells, and initiates an inflammatory response, which further damages the surrounding tissues. Contact with liquid ammonia (not ammonium salts) results in cryogenic injury in addition to the alkali burns. Airway blockage and respiratory insufficiency may be lethal outcomes of exposure to anhydrous ammonia vapors or concentrated aerosols. Ingestion of concentrated ammonium solutions may produce severe burns and hemorrhage of the upper gastrointestinal tract. Survival of the initial insult may be compromised by infections, scarring, and other complications that may develop days or weeks following inhalation or ingestion. Effects that have been observed in humans exposed to ammonia gas and ammonium salt aerosols have also been observed in animals. Hepatic and renal effects have also been reported in animals and humans; however, ammonia does not appear to be a primary liver or kidney toxicant.

Increased systemic ammonia/ammonium salts/ion, or hyperammonemia, is generally not seen following inhalation or dermal exposure, but can result from ingestion and from certain disease states such as cirrhosis of the liver, acute liver failure, and congenital deficiencies of any of the urea cycle enzymes. Liver disease can result in decreased metabolism of ammonia with resultant increased levels of ammonia in the bloodstream and in the brain, which can produce neurological effects such as seizures and coma, and eventually death. In chronic liver failure, arterial ammonia concentrations may reach approximately 3.6 mg/L, whereas arterial ammonia in acute liver failure may rise as high as 8 mg/L. The most likely and significant effects of exposure to elevated levels of ammonia are discussed below.

Respiratory Effects. Ammonia is an upper respiratory irritant in humans. Exposures to levels exceeding 50 ppm result in immediate irritation to the nose and throat; however, tolerance appears to develop with repeated exposure. Exposure to an air concentration of 250 ppm is bearable for most persons for 30–60 minutes. Acute exposure to higher levels (500 ppm) have been shown to increase respiratory minute volume. Accidental exposures to concentrated aerosols of ammonium salts or high concentrations of ammonia gas have resulted in nasopharyngeal and tracheal burns, airway obstruction and respiratory distress, and bronchiolar and alveolar edema. Ammonia vapor readily dissolves in the moisture present on the skin, eyes, oropharynx and lungs forming ammonium hydroxide which dissociates to yield hydroxyl ions. Chronic occupational exposure to low levels of airborne ammonia (<25 ppm) had little effect on pulmonary function or odor sensitivity in workers at some factories, but studies of farmers exposed to ammonia and other pollutants in livestock buildings indicated an association between exposure to pollutants, including ammonia, and an increase in respiratory symptoms (such as bronchial reactivity/hyperresponsiveness, inflammation, cough, wheezing, or shortness of breath) and/or a decrease in lung function parameters. The contribution of ammonia to these respiratory symptoms is unclear.

Dermal Effects. Skin is extremely sensitive to airborne ammonia or ammonia dissolved in water. The topical damage caused by ammonia is probably due mainly to its reactivity and irritation properties. Its high water solubility allows it to dissolve in moisture on these surfaces, react with fatty substances, be absorbed into deeper layers, and inflict extensive damage. Reports of skin damage in humans are numerous, but good quantitative data are lacking. The severity of the damage is proportional to the concentration and duration of exposure; flushing with water immediately after contact alleviates or prevents effects.

Dermal exposures to liquid ammonia or concentrated solutions and/or ammonia gas are frequently occupationally related and produce cutaneous burns, blisters, and lesions of varying degrees of severity. Unlike acid burns, which cause a coagulation necrosis, ammonia causes alkali burns, resulting in liquification of the tissue and deeper penetrations. Burns can be severe enough to require skin grafting, and loss of the epidermal layer increases body fluid loss and incidence of infection. While most ammonia exposures are occupational, household products containing ammonia can also cause dermal injury. Several cases of young children (2–3 years old) who bit into ammonia pellets/capsules and sustained oral and esophageal lesions have been reported in the literature.

Very limited animal data regarding dermal effects of exposure to ammonia support the findings in humans.

Ocular Effects. Reported ocular effects in humans following ammonia gas exposure increased in severity with dose and duration. Good quantitative data are lacking, but symptoms progress as follows: inflamed eyes, lacrimation, swelling of the eyelids, hyperemic conjunctiva, blurred vision, possible transient blindness, corneal abrasions, and sustained corneal damage. Ammonia is slightly irritating to human eyes in a brief exposure at concentrations of 100 ppm, and immediately irritating to the eyes and throat at 698 ppm. Exposure to an air concentration of 250 ppm is bearable for most persons for 30–60 minutes.

Limited animal data regarding ocular effects of exposure to ammonia support the findings in humans.

Neurological Effects. Neurological effects in humans following inhalation or dermal exposure to ammonia are usually limited to blurred vision, most likely due to direct contact, but more severe exposures, which result in significant elevation of blood ammonia levels (hyperammonemia), can result in diffuse nonspecific encephalopathy, muscle weakness, decreased deep tendon reflexes, and loss of consciousness. Hyperammonemia in humans can result from certain disease states such as cirrhosis of the liver, acute liver failure, and congenital deficiencies of any of the urea cycle enzymes; hyperammonemia may lead to encephalopathy. Some have suggested that ammonia may be involved in the generation of the symptomatology and progression of Alzheimer's disease as a result of pathological ammonia metabolism in the brain. Cerebral edema and herniation and intracranial hypertension have been noted in animal models of hyperammonemia. The mechanism of ammonia-induced encephalopathies has not been definitively elucidated. It is thought to involve the alteration of glutamate metabolism in the brain with resultant increased activation of N-methyl-D-aspartate (NMDA) receptors, which causes decreased protein kinase *C*-mediated phosphorylation of Na^+/K^+ ATPase, increased activity of Na^+/K^+ ATPase, and depletion of ATP. Additional evidence of altered energy levels includes changes in some TCA cycle-associated components including acetoacetate, and NAD^+/NADH ratio, 2-oxoglutarate, and 3-hydroxybutarate. This reduced ATP level may be involved in ammonia-induced coma and death. A disruption in neurotransmission has also been suggested by alteration of brain tubulin, which is an essential component of the axonal transport system.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

- An MRL of 1.7 ppm has been derived for acute-duration inhalation exposure (14 days or less) to ammonia.

This MRL is based on a lowest-observed-adverse-effect level (LOAEL) of 50 ppm for mild irritation to the eyes, nose, and throat in humans exposed to ammonia as a gas for 2 hours (Verberk et al. 1977). In that study, a group of 16 subjects were tested, 8 of them (experts) knew the effects of ammonia from the literature, but had no personal contact, whereas the remaining 8 subjects (non-experts) were students from a non-science faculty and were not familiar with ammonia or experiments in laboratory situations. All members of a group were exposed on the same day to one of the concentrations tested (50, 80, 110, or 140 ppm). The testing was repeated with a 1-week interval. Immediately before and after exposure, vital capacity, forced expiratory volume, and forced inspiratory volume were measured. During exposure, each subject recorded subjective feelings every 15 minutes as no sensation (0), just perceptible (1), distinctly perceptible (2), nuisance (3), offensive (4), or unbearable (5). No statistical analysis was performed and there was no group exposed to air only. Results of the pulmonary function tests after exposure were not statistically significantly different from pre-exposure values. For the non-experts, there was a clear increase in the number of reported symptoms for smell, eye irritation, throat irritation, cough, and general discomfort as the exposure concentration increased. The latter was not as clear for the experts. It should also be mentioned that the subjective responses appeared more pronounced in the non-expert group than in the expert group. The LOAEL was divided by an uncertainty factor of 30 (10 to protect sensitive individuals and 3 for the use of a minimal LOAEL). A study of piggerie workers exposed to a mean level of 7.9 ppm ammonia measured pulmonary function change over a workshift; a small but borderline significant decrease in pulmonary function was noted (Heederik et al. 1990). This study was not used as a basis for MRL derivation because the workers were also exposed to other potential respiratory toxicants (dust and endotoxins). Although the Verberk et al. (1977) study has limitations (no statistical analysis, subjective end points, no control group), it demonstrates that concentrations of 50 ppm ammonia produce minimal discomfort in healthy members of the general population and therefore, should be avoided. A more detailed discussion of additional information supporting the findings of Verberk et al. (1977) is presented in Appendix A.

No intermediate-duration inhalation MRL was derived for ammonia. The only available intermediate-duration inhalation study in humans is that of Ferguson et al. (1977). In that study, a group of 6 healthy

volunteers, not previously accustomed to working in an ammonia environment, were exposed 5 days/week to 25 ppm (2 hours/day), 50 ppm (4 hours/day), or 100 ppm (6 hours/day) of ammonia, or to 50 ppm of ammonia 6 hours/day for 6 weeks. End points monitored included subjective and objective measures of eye and throat irritation as well as pulse rate, respiration rate, pulmonary function (FVC, FEV), assessment of neurological function (reflex, balance, and coordination), and body weight. The exposure protocol consisted of a pre-exposure evaluation by a physician, 3 hours of exposure (this conflicts with exposure data on table 2 of the study and mentioned above), a mid-point physician's observation, lunch break, 3 additional hours of exposure, and a third physician's observation 30 minutes after exposure ceased. The conjunctiva and mucosa of the nose and throat were examined by a physician before and after each daily exposure and the degree of irritation noted was described as mild, moderate, or marked. Exposure to ammonia had no significant effect on the measures of respiratory function or in the neurological tests conducted. The results of the evaluations of irritation conducted by the physician showed no significant differences between the exposure groups, including the 0 ppm exposure group (pre-exposure). All subjects experienced some watering of the eyes and a sensation of dryness in the nose and throat, and there was one observation of definite redness in the mucosa of the nose after a 6-hour exposure to 100 ppm during which time, there was an excursion to 200 ppm ammonia. No redness was observed in this subject the following morning. Throughout the study, the physician observed 6 cases of eye irritation, 20 of nose irritation, and 9 of throat irritation, and most cases appeared to have occurred the first week of the study during exposure to 50 ppm. It is difficult to determine in this study a no-observed-adverse-effect level (NOAEL) or LOAEL for irritation due to the different exposure durations experienced by the subjects. In general, studies in animals have used higher exposure concentrations and the overall quality of the studies is less than desirable. For ammonia, a corrosive irritant gas that affects the portal of entry and produces irritation of eyes and respiratory tract, use of human data should be preferred over animal studies.

- An MRL of 0.1 ppm has been derived for chronic-duration inhalation exposure (365 days or more) to ammonia.

This MRL supersedes the previous chronic inhalation MRL of 0.3 ppm derived in the 2002 draft for public comment version of this profile. The MRL is based on a NOAEL of 9.2 ppm for sense of smell, prevalence of respiratory symptoms (cough, bronchitis, wheeze, dyspnea, and others), eye and throat irritation, and lung function parameters (FVC, FEV_1, FEV_1/FVC, FEF_{50}, and FEF_{75}) in humans exposed for an average of 12.2 years in a soda ash plant (Holness et al. 1989); no LOAEL was determined. The cohort consisted of 52 workers and 35 controls. The subjects were assessed on two workdays: on the first workday of their workweek and on the last workday of their workweek. Spirometry was performed at the

beginning and end of each work shift, so that each worker had four tests done. To determine the exposure levels, exposed and control workers were sampled over one work shift; the average sample collection period was 8.4 hours. All of the participants in the study were males. Analysis of the results showed no significant differences in the prevalence of reported symptoms, but the exposed workers reported that exposure in the plant aggravated some of their reported symptoms (cough, wheeze, nasal complaints, eye irritation, and throat discomfort). Odor threshold was not affected by exposure to ammonia and there were no significant differences in baseline lung functions between exposed and control subjects. Analysis of each worker separately showed no significant relationship between the level of ammonia exposure and changes in lung function. Also, when the workers were divided into groups of individuals that were exposed to low (<6.25 ppm), medium (6.25–12.5 ppm), and high (>12.5 ppm) ammonia levels, no significant association was found between reporting of symptoms, decline in baseline function, or increasing decline in function over the work shift and exposure to ammonia. Furthermore, no association was evident between increasing years of exposure and decreasing lung function. However, the power of the indices of both level and length of exposure is low because only eight workers were in areas with relatively high ammonia exposure. The MRL was calculated by adjusting the mean TWA exposure concentration of 9.2 ppm for continuous exposure (8/24 hours x 5/7 days) and dividing by an uncertainty factor of 10 to protect sensitive individuals. A modifying factor of 3 was added for the lack of reproductive and developmental studies.

Oral MRLs

No oral MRLs were derived for ammonia because of two main reasons. In the first place, the overall quality and/or usefulness of the oral database is limited. The only human acute oral studies available were case reports with no exposure levels (Klein et al. 1985; Klendshoj and Rejent 1966; Lopez et al. 1988). Animal studies were limited to a food intake study (Noda and Chikamori 1976), single-exposure studies with no effect, serious effects, or unsupported effects (Benyajati and Goldstein 1975; Koenig and Koenig 1949), a gavage study that lacked study details (Boyd and Seymour 1946), and a 6-day drinking water study with effects at high levels (Barzel 1975). Rats exposed to 3,102 mg NH_4^+/kg/day in the diet and drinking water for 7 days had statistically significantly reduced body weight gain (64% less) compared to a control group that consumed only 22 mg NH_4^+/kg/day (Boyano-Adánez et al. 1996). Such a high dose of ammonium (as acetate) is equivalent to a 70 kg human ingesting approximately 1.4 lb of ammonium acetate daily. No human studies or reports of intermediate-duration oral exposure to ammonia were located. Intermediate-duration animal studies have reported decreases in body weight gain in rats exposed via drinking water (Gupta et al. 1979) or diet (Boyano-Adánez et al. 1996). It should be

mentioned that Gupta et al. (1979) administered ammonium sulfamate to the rats. Ammonium sulfamate is an herbicide whose herbicide properties reside in the sulfamate portion of the salt and for which there is little toxicity information in the open literature. The EPA (IRIS 2004) has derived an oral RfD for the sulfamate moiety based on the results of Gupta et al. (1979). Following gavage administration of ammonium salts, bone, blood pressure, adrenal gland, and renal effects have been observed in early studies, generally inadequate by current standards (Bodansky et al. 1932; Fazekas 1939; Seegal 1927). No chronic-duration oral data were located.

An additional reason not to derive oral MRLs for ammonia is because of the role played by the anion of the salt administered. Briefly, in many animal studies, the animals were administered ammonium chloride. Ammonium chloride is commonly used to induce metabolic acidosis in experimental animals. The acidosis is due to the formation of hydrogen ions from the metabolism of ammonium ions to urea. WHO (1986) notes that the ingestion of ammonium chloride in doses around 500–1,000 mg/kg/day for 1–8 days (longer treatment would worsen the condition) has induced metabolic acidosis in mice, guinea pigs, rats, rabbits, and dogs. Metabolic acidosis can result in a variety of nonspecific changes in neurological, cardiovascular, pulmonary, gastrointestinal, and musculoskeletal function, as well as in changes in hematological and clinical chemistry parameters. Acidosis following the administration of ammonium chloride is due to the formation of hydrogen chloride and although it will occur with any ammonium salt, the degree of acidosis (and associated consequences) will be determined by the ability of the kidneys to excrete the specific anion. DeSousa et al. (1974) showed that administration of hydrochloric acid to dogs induced a significantly greater decrease in plasma bicarbonate than administration of equivalent quantities of H^+ as nitric or sulfuric acid. This means that it would be inappropriate to extrapolate findings obtained with ammonium chloride (or any ammonium salt) to equivalent amounts of ammonium, but derived from a different salt.

Finally, as discussed by WHO (1986), the amount of excess ammonia (over and above the amount normally produced in the body) that can be safely ingested and assimilated is difficult to define. However, data from human and animals suggest that that amount may be substantial based on the existence of various efficient ways by which the body can dispose of ammonia.

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 ammonia. 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.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for ammonia. 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.

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

There are many reports in the literature of human deaths resulting from inhalation of ammonia (Arwood et al. 1985; Burns et al. 1985; Close et al. 1980; Couturier et al. 1971; George et al. 2000; Heifer 1971; Price et al. 1983; Sobonya 1977; Walton 1973; Weiser and Mackenroth 1989; Yang et al. 1987). Most of these reports are of acute accidental exposure to ammonia gas. A review of the early literature on ammonia toxicity cites acute exposure to 5,000–10,000 ppm as being rapidly fatal in humans (Henderson and Haggard 1927; Mulder and Van der Zalm 1967) and exposure to 2,500–4,500 ppm as being fatal in about 30 minutes (Helmers et al. 1971; Millea et al. 1989). Immediate deaths resulting from acute exposure to ammonia appear to be caused by airway obstruction while infections and other secondary complications are lethal factors among those who survive for several days or weeks. Chemical burns and edema of exposed tissues, including the respiratory tract, eyes, and exposed skin, are often observed after exposure to lethal levels. Post-mortem findings in the fatal case described by Walton (1973) included extensive edema and burns affecting the mouth, faces, trunk, arms, and upper part of the trunk. The airway at the larynx was almost blocked and the lungs were greatly distended and congested. Histological examination of the lungs showed acute congestion and edema. The bronchial walls were stripped of their epithelial lining, and some smaller bronchi contained plugs of debris, which included epithelial cells, red blood cells, and dust cells. No reports of human death due to intermediate or chronic exposure to ammonia were located.

Studies in animals indicate that the acutely lethal exposure concentration depends on the exposure duration. The lethal concentration in rats and mice increases 5–10 times as the exposure duration decreases from 16 hours to several minutes (Hilado et al. 1977, 1978; Kapeghian et al. 1982; Morgan 1997; Prokop'eva et al. 1973; Weedon et al. 1940). Exposure frequency also appears to be an important factor in determining lethality. Continuous exposure to 653 ppm for 25 days resulted in nearly 64% lethality in rats, whereas intermittent exposure (5 days/week, 8 hours/day) to nearly twice this concentration was tolerated for 42 days (Coon et al. 1970). It appears that male rats are more sensitive than female rats to the lethal effects of ammonia (Appelman et al. 1982; Stupfel et al. 1971). Animals exposed to acutely lethal concentrations show severe lesions in the respiratory tract that are similar to those observed in humans. Less severe lesions of the liver, heart, and kidney have been observed following continuous long-term exposure to lethal concentrations in rats, guinea pigs, rabbits, and dogs (Coon et al. 1970). However, these may represent secondary complications from chronic respiratory tract injury.

3.2.1.2 Systemic Effects

Respiratory Effects. Ammonia is an upper respiratory irritant in humans. Exposures to levels exceeding 30 ppm result in immediate irritation to the nose and throat (Industrial Bio-Test Laboratories 1973; MacEwen et al. 1970; Sekizawa and Tsubone 1994; Verberk 1977). Four out of six human subjects described moderate irritation of the nose and eyes when exposed to 50, but not 30, ppm ammonia gas for 10 minutes (MacEwen et al. 1970). Twenty to 30% of subjects exposed to 72, but not 50, ppm ammonia gas for 5 minutes experienced eye, nasal, and throat irritation (Industrial Bio-Test Laboratories 1973). However, tolerance appears to develop with repeated exposure (Sekizawa and Tsubone 1994; Verberk 1977). Thus, subjects exposed to 50 ppm ammonia 6 hours/day, 5 days/week for 6 weeks experienced nose and throat irritation only during the first week (Ferguson et al. 1977). Acute exposure to higher levels (500 ppm) has been shown to alter respiratory minute volume (Cole et al. 1977; Silverman et al. 1949). Buff and Koller (1974) suggest that this is due to an effect on "irritant receptors" in the lungs resulting in increased activity of reflex respiratory muscles. This mechanism is also suggested by Cole et al. (1977), who exposed men to 100–331 ppm ammonia gas for 8–11 minutes while they were exercising on a stationary bicycle. Respiratory minute volume was decreased at concentrations of 150–331 ppm (but not at 100 ppm), and tidal volume was increased at 100 ppm ammonia, but decreased at higher concentrations (Cole et al. 1977). Accidental exposures to concentrated aerosols of ammonium solutions, high concentrations of ammonia gas, or anhydrous ammonia fumes have resulted in nasopharyngeal and tracheal burns, airway obstruction and respiratory distress, and bronchiolar and alveolar edema (Burns et al. 1985; Close et al. 1980; Couturier et al. 1971; de la Hoz et al. 1996; George et al. 2000; Hatton et al. 1979; Heifer 1971; Kass et al. 1972; Kerstein et al. 2001; Latenser and Lucktong 2000; Leduc et al. 1992; Millea et al. 1989; Morgan 1997; O'Kane 1983; Price et al. 1983; Sobonya 1977; Taplin et al. 1976; Walton 1973; Weiser and Mackenroth 1989). Chronic occupational exposure (about 14 years) to low levels of airborne ammonia (12.5 ppm) had no significant effect on pulmonary function or odor sensitivity in a group of workers at a soda ash factory compared to a control group from the same factory that was not exposed to ammonia (Holness et al. 1989). An acute-duration inhalation MRL of 1.7 ppm was derived from the Verberk (1977) study, and a chronic inhalation MRL of 0.1 ppm was derived from the Holness et al. (1989) study; MRLs are presented in Table 3-1 and Figure 3-1 and are discussed in Section 2.3.

One human study with somewhat controlled exposure to ammonia showed that pulmonary function was not affected by low levels (25–100 ppm) of ammonia (Ferguson et al. 1977). Transient nose and throat

Table 3-1 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Human	1 d 0.5 hr/d				5000 (rapidly fatal)	Henderson & Haggard 1927
2	Rat	1 d 15 min/d				17401 (LC50)	Prokop'eva et al. 1973
3	Rat	1 d 16 hr/d				1000 (LC50)	Weedon et al. 1940
4	Mouse	1 d 30 min/d				21430 (LC50)	Hilado et al. 1977
5	Mouse	1 d 1 hr/d				4230 (LC50)	Kapeghian et al. 1982
6	Mouse	1 d 60 min/d				11299 (LC50)	Prokop'eva et al. 1973
7	Mouse	1 d 16 hr/d				1000 (LC50)	Weedon et al. 1940

Table 3-1 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
8	Rabbit	1 d 1 hr/d				5025 (LC50)	Boyd et al. 1944
9	Cat	1 d 1 hr/d				5025 (LC50)	Boyd et al. 1944
	Systemic						
10	Human	8-11 min	Resp	100 M	150 M (decreased minute volume; increased tidal volume)		Cole et al. 1977
11	Human	5 min	Resp	50	72 (nasal and throat irritation)		Industrial Bio-Test Laboratories, Inc. 1973
12	Human	10 min	Resp	30	50 (moderate nasal irritation)		MacEwen et al. 1970

Table 3-1 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
13	Human	1 d 30 min/d	Resp		500 M (nasal and throat irritation; increased minute volume and respiratory rate)		Silverman et al. 1949
			Cardio	500 M			
			Hemato	500 M			
			Ocular		500 M (lacrimation)		
14	Human	1 d 2 hr/d	Resp		50[b] (urge to cough; irritation to nose and throat)		Verberk 1977
			Ocular		50 (irritation to eyes)		
15	Rat (Sherman)	4 wk 24 hr/d	Ocular		100 (eye irritation)		Broderson et al. 1976

Table 3-1 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
16	Rat (OFA)	1 wk 24 hr/d	Resp		500 (irritation)		Richard et al. 1978a
			Renal		500 (increased kidney weight)		
			Bd Wt		500 (body weight and food intake decreased 21%)		
17	Rat	7 d	Resp	714			Schaerdel et al. 1983
			Gastro	714			
			Hemato		15 (slight increase blood pO2)		
			Renal	714			
			Dermal	714			
			Other	714			

Table 3-1 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
18	Mouse (ICR)	1 d 1 hr/d	Resp		3440 M (dyspnea; nasal irritation)	4220 M (congestive intraalveloar hemorrhage, 24% increased relative lung weight)	Kapeghian et al. 1982
			Hepatic			3440 M (degenerative changes; increased relative liver weight)	
			Bd Wt	3440 M	4220 M (12% reduction in body weight)		
19	Dog (Beagle)	1 wk 5 d/wk 8 hr/d	Resp	218.6 M	1085.7 M (temporary dyspnea during first week of exposure)		Coon et al. 1970
20	Rabbit (New Zealand)	1 wk 5 d/wk 8 hr/d	Resp	218.6 M	1085.7 M (temporary dyspnea during first week of exposure)		Coon et al. 1970
			Ocular	218.6 M	1085.7 M (temporary lacrimation)		
21	Rabbit	1 d 1 hr/d	Resp			5000 (acute pulmonary edema)	Richard et al. 1978b
			Cardio		2500 (bradycardia)	5000 (hypertension, acidosis, EKG change)	

Table 3-1 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
22	Cat (Mongrel)	1 x 10 min (IT)	Resp		1000 (dyspnea; rhonchi; rales)		Dodd and Gross 1980
23	Pig (Belgian Landrace)	6 d	Resp	50 M	100 M (decreased pulmonary vascular response to endotoxin challenge)		Gustin et al. 1994
			Cardio	50 M	100 M (decreased pulmonary vascular response to endotoxin challenge)		
			Hemato	100 M			
			Endocr	100 M			
			Bd Wt	25 M	50 M (3% weight loss)		
24	Pig (Duroc)	1-2 wk	Resp	10	50 (frequent coughing)		Stombaugh et al. 1969
			Dermal	10	50 (oral and nasal irritation)		
			Bd Wt	10	50 (reduced weight gain and food intake)		

[a]

Table 3-1 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Immuno/ Lymphoret						
25	Mouse	7 d 24 hr/d			500 M (decreased resistance to infection)		Richard et al. 1978a
26	Pig (Belgian Landrace)	6 d		50 M	100 M (decreased pulmonary response to endotoxin challenge)		Gustin et al. 1994
	Neurological						
27	Rat	1 d 6 hr/d			100 (sensory irritation)		Tepper et al. 1985
28	Mouse	1 d 6 hr/d			100 (sensory irritation)		Tepper et al. 1985
	INTERMEDIATE EXPOSURE						
	Death						
29	Rat	90 d				641.6 (98% lethality)	Coon et al. 1970

Table 3-1 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Systemic						
30	Human	6 wk 5 d/wk 6 hr/d	Resp	25	50 (transient irritation of nose and throat)		Ferguson et al. 1977
			Cardio	100			
			Ocular	25	50 (transient eye irritation)		
31	Monkey (Squirrel monkey)	6 wk 5 hr/wk 8 hr/d	Resp		218.6 M (focal pneumonitis)		Coon et al. 1970
			Cardio	1085.7 M			
			Hemato	1085.7 M			
			Hepatic	1085.7 M			
			Renal	1085.7 M			
			Dermal	1085.7 M			
32	Rat (Sherman)	5-10 wk 24 hr/d	Resp		250 (nasal lesions, epithelial hyperplasia)		Broderson et al. 1976

Table 3-1 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
33	Rat	6 wk 5 d/wk 8 hr/d	Resp	218.6	1085.7	(nonspecific inflammation)			Coon et al. 1970
			Cardio	1085.7					
			Hemato	1085.7					
			Hepatic	1085.7					
			Renal	1085.7					
			Ocular	1085.7					
34	Rat (Sprague-Dawley)	90 or 114 d	Resp	179.1	369.4	(mild nasal discharge in 25% of animals)	641.6	(interstitial pneumonitis)	Coon et al. 1970
			Cardio	369.4			641.6	(myocardial fibrosis)	
			Hepatic	369.4	641.6	(fatty changes of liver plate cells)			
			Renal	369.4			641.6	(renal tubular calcification)	

Table 3-1 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
35	Gn Pig	6 wk 5 d/wk 8 hr/d	Resp	218.6	1085.7 (non specific inflammation)		Coon et al. 1970
			Cardio	1085.7			
			Hemato	1085.7			
			Hepatic	1085.7			
			Renal	1085.7			
			Dermal	1085.7			
36	Gn Pig (Hartley)	3 wk 24 hr/d	Resp	90			Targowski et al. 1984
			Hemato	90			
			Ocular	90			
			Bd Wt	90			

Table 3-1 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
37	Gn Pig	18 wk 5 d/wk 6 hr/d	Resp	170			Weatherby 1952
			Cardio	170			
			Gastro	170			
			Hemato		170 (increased hemosiderin)		
			Hepatic		170 (congestion)		
			Renal		170 (congestion)		

Table 3-1 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
38	Rabbit	114 d	Resp	57			Coon et al. 1970
			Cardio	57			
			Hemato	57			
			Hepatic	57			
			Renal	57			
			Dermal	57			
39	Pig (NS)	4 wks	Resp		100 (excessive nasal secretion, coughing, tracheal inflammation)		Drummond et al. 1980
			Ocular		50 (excessive lacrimation)		
			Bd Wt	50	100 (18.6% reduction in final body weight)		
	Immuno/ Lymphoret						
40	Rat (Sherman and Fischer)	4 wk 24 hr/d			25 (increased severity of infection by mycoplasma)		Broderson et al. 1976

Table 3-1 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
41	Rat	3 wk 24 hr/d			500 M (reduced resistance to infection)		Richard et al. 1978a
42	Gn Pig (Hartley)	3 wk 24 hr/d			90 (significantly reduced delayed-type response to tuberculin)		Targowski et al. 1984
				50			
43	Pig (NS)	31-45 d 24 hr/d			100 (decreased serum concentration of gamma globulin)		Neumann et al. 1987
	Neurological						
44	Monkey (Squirrel monkey)	6 wk 5 hr/wk 8 hr/d		1085.7 M			Coon et al. 1970
45	Gn Pig	6 wk 5 d/wk 8 hr/d		1085.7			Coon et al. 1970

Table 3-1 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
46	Pig	4 wks		50	100 (lethargy)		Drummond et al. 1980
	CHRONIC EXPOSURE						
	Systemic						
47	Human	12.2 yr 5 d/wk 8 hr/d	Resp	9.2[c]			Holness et al. 1989
			Ocular	9.2			

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

b Used to derived an acute-duration inhalation MRL of 1.7 ppm; the MRL was derived by dividing the LOAEL of 50 ppm by an uncertainty factor of 30 (10 for variation in sensitivity among humans and 3 for use of a minimal LOAEL).

c Used to derive a chronic-duration inhalation MRL of 0.1 ppm; the MRL was derived by adjusting the NOAEL of 9.2 ppm for continuous exposure (9.2 x 8/24 hours x 5/7 days) and dividing by an uncertainty factor of 30 (10 for the protection of sensitive individuals, and 3 for the lack of reproductive and developmental studies).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; gastro = gastrointestinal; hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; metab = metabolic; min = minute; mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s)

Figure 3-1. Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation

Acute (≤14 days)

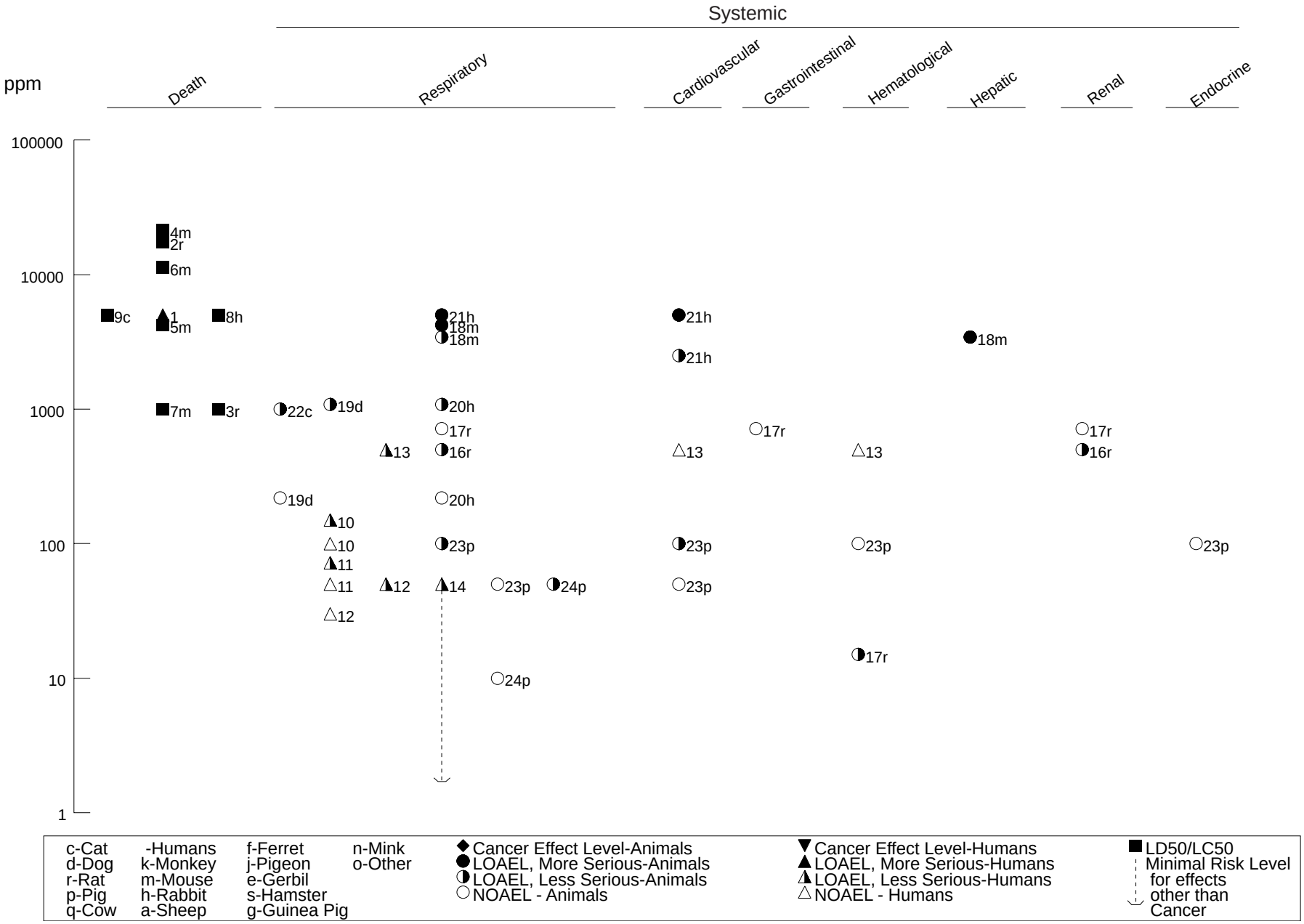


Figure 3-1. Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (*Continued*)

Acute (≤14 days)

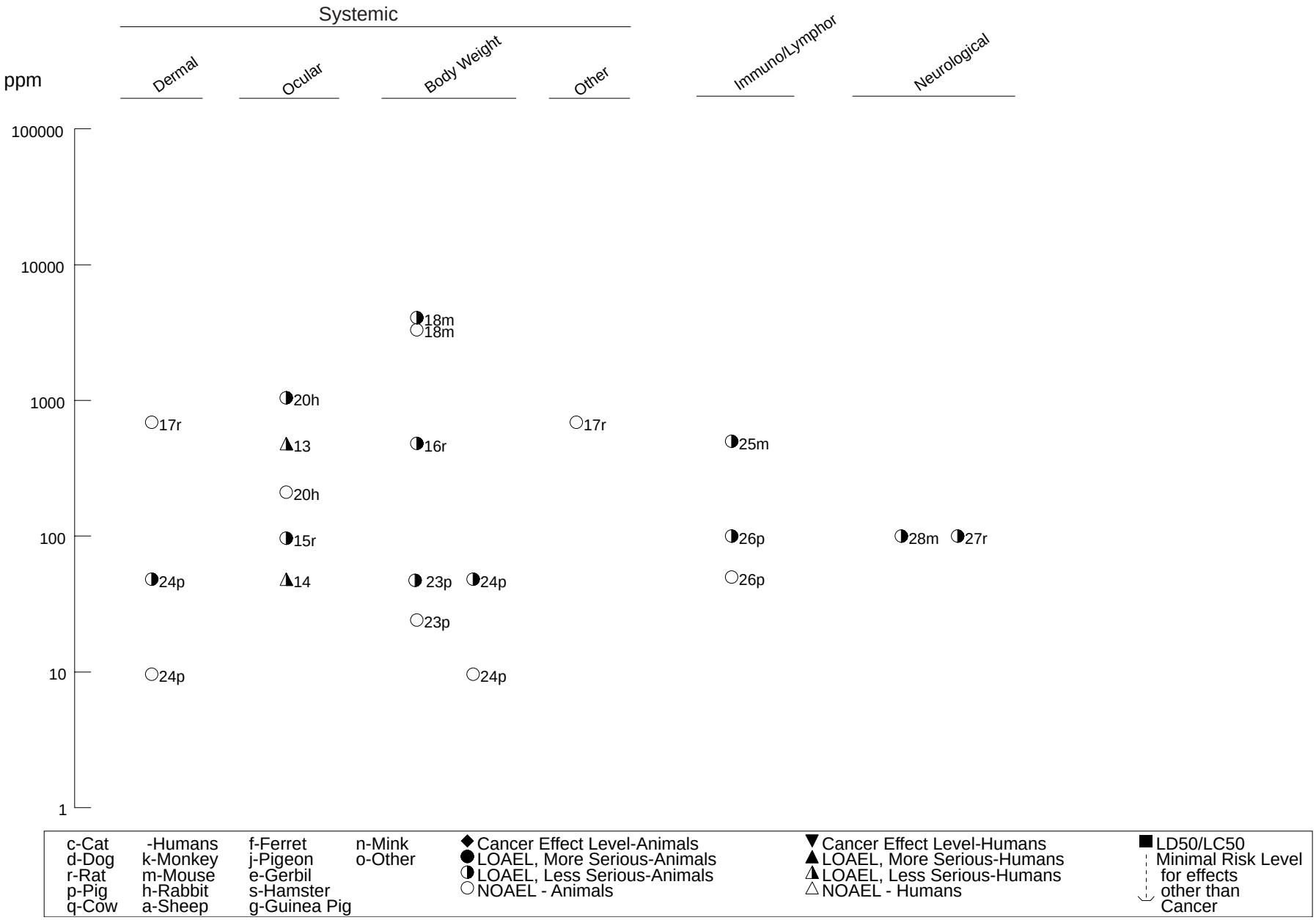


Figure 3-1. Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (*Continued*)

Intermediate (15-364 days)

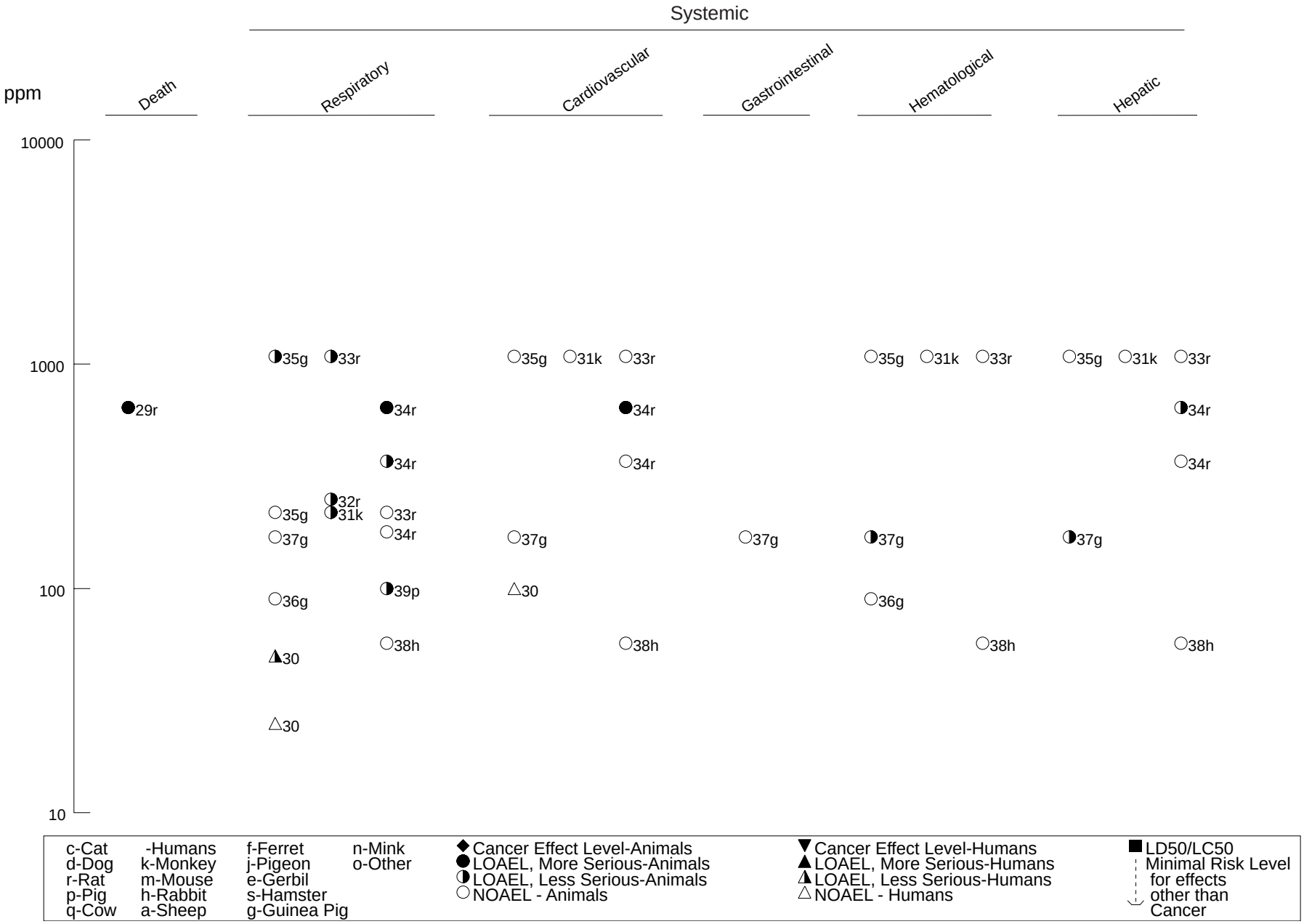


Figure 3-1. Levels of Significant Exposure to Ammonia And Ammonium Compounds - Inhalation (*Continued*)

Intermediate (15-364 days)

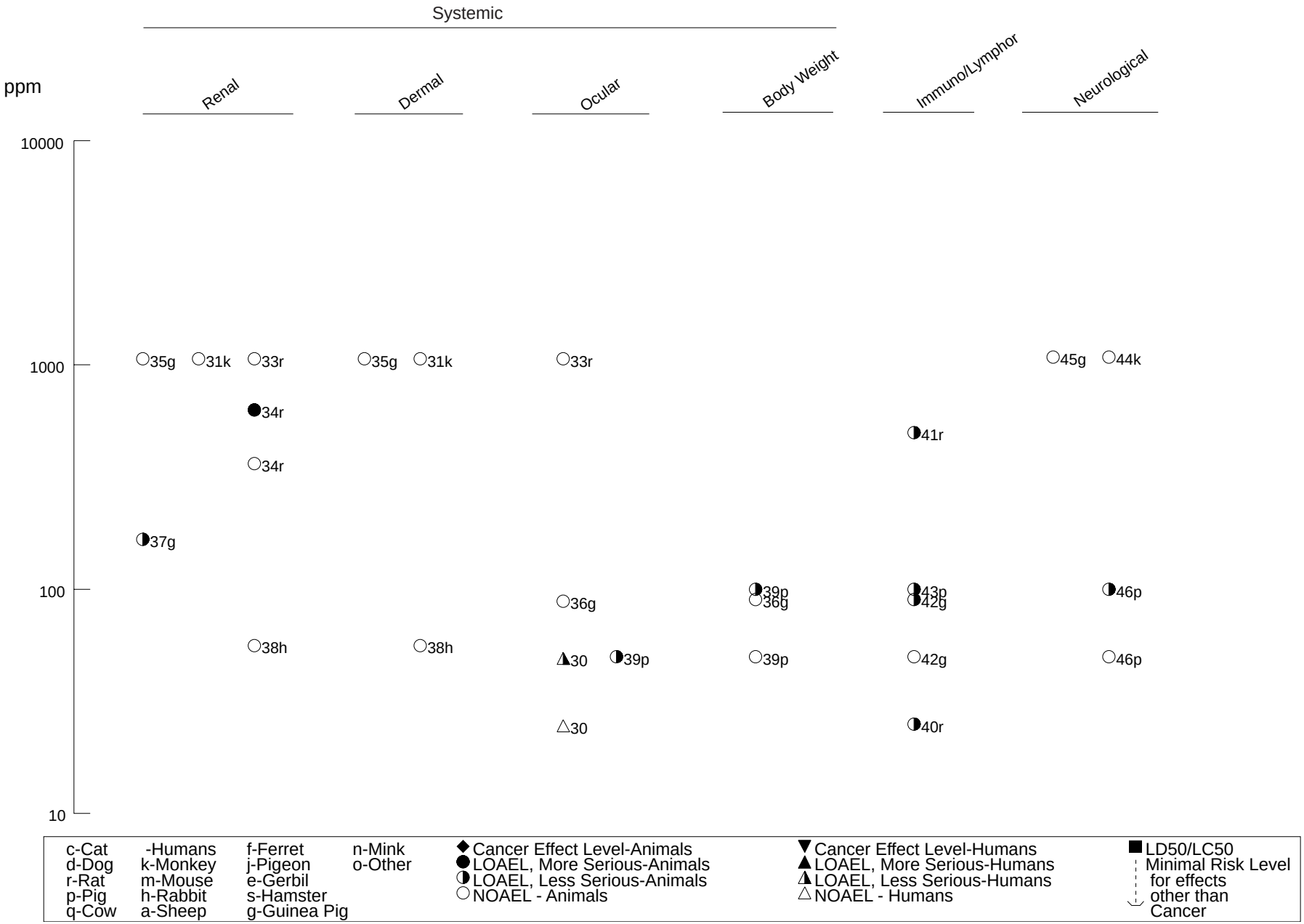
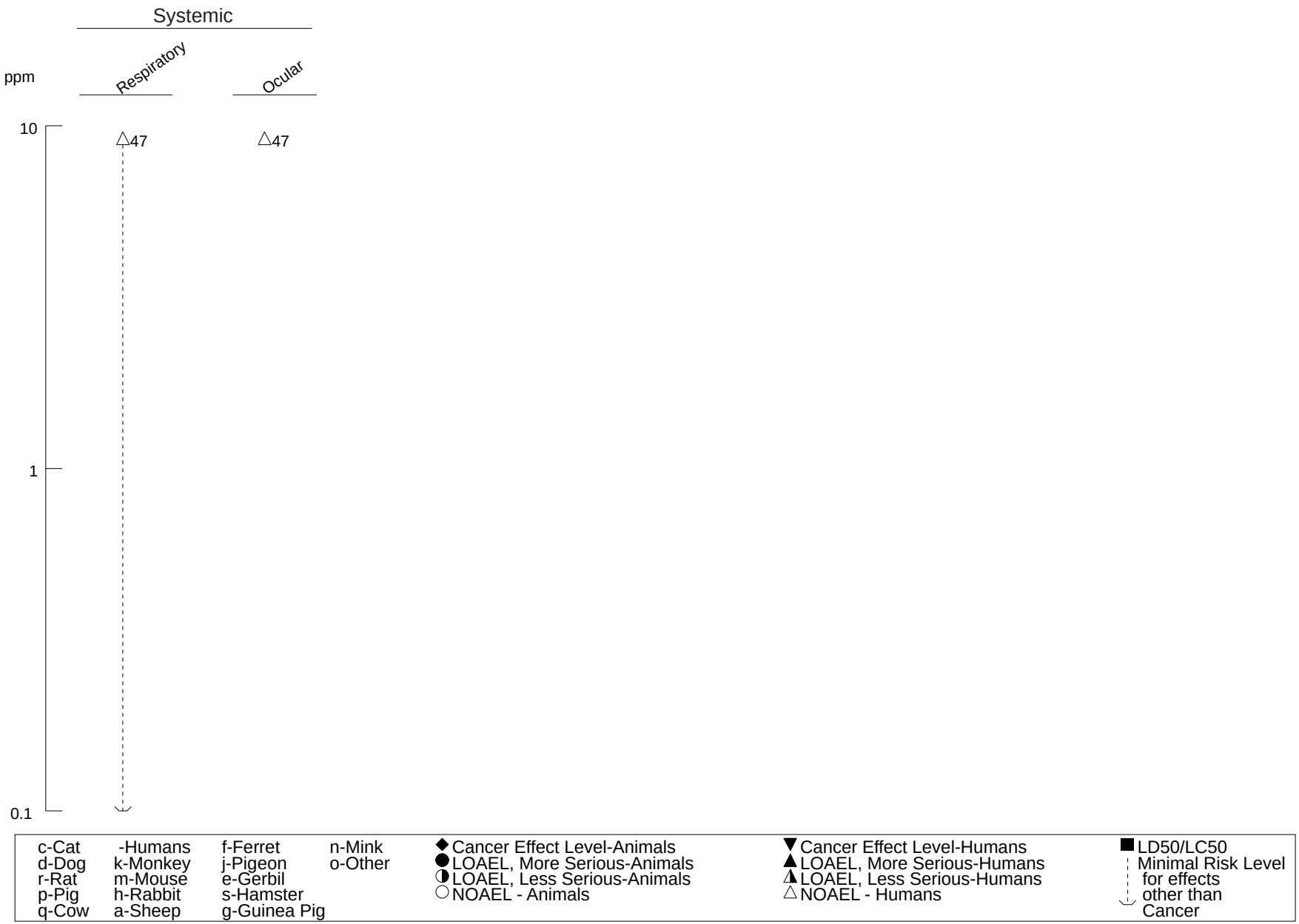


Figure 3-1. Levels of Significant Exposure to Ammonia And Ammonium Compounds- Inhalation (*Continued*)

Chronic (≥365 days)



irritation was noted the first week of exposure in male and female volunteers exposed to 50 ppm, but not 25 ppm ammonia 5 days/week, for 6 weeks. No significant differences were noted between exposed and control groups for pulmonary function tests, physical examinations, or performance of normal job duties (Ferguson et al. 1977).

A number of occupational cohort studies that examined farmers who worked in enclosed livestock buildings have been conducted. These studies all included measurements of ammonia in the livestock confinement buildings, as well as measurements of one or more of the following: total dust, respirable dust, carbon dioxide, total endotoxins, respirable endotoxins, fungi, bacteria, and molds (Choudat et al. 1994; Cormier et al. 2000; Donham et al. 1995, 2000; Heederik et al. 1990, 1991; Melbostad and Eduard 2001; Reynolds et al. 1996; Vogelzang et al. 1997, 2000). Of the pollutants measured, ammonia and dust were most frequently associated with respiratory effects, many of which were temporary and disappeared with cessation of exposure. Ammonia levels ranged from 2.3 to 20.7 ppm and total dust levels from 0.04 to 5.64 mg/m^3. Most of these studies reported an association between exposure to pollutants, including ammonia, in livestock confinement buildings and an increase in respiratory symptoms (such as bronchial reactivity/hyperresponsiveness, inflammation, cough, wheezing, or shortness of breath) and/or a decrease in pulmonary function (such as forced expiratory volume in the first second [$FEV_{1.0}$], maximum expiratory flow rates [MEF_{50} and MEF_{75}], and maximal mid-expiratory flow rate [MMEF]) (Choudat et al. 1994; Cormier et al. 2000; Donham et al. 1995, 2000; Heederik et al. 1990; Reynolds et al. 1996; Vogelzang et al. 1997, 2000). One study, however, reported correlations only between total dust, fungal spore, and endotoxin mean exposure levels and task-specific prevalences (Melbostad and Eduard 2001). Another study reported no significant correlations between lung function or chronic respiratory symptoms and dust or ammonia levels, but suggested that endotoxins and bacteria levels may play a role (Heederik et al. 1991). Most studies adjusted for confounding factors, such as smoking and number of years worked on a farm, in their statistical analyses. All of the studies concluded that prevalence of respiratory symptoms of some type was higher in the farmer cohort than in the respective control group. It is not clear from these studies what the contribution of ammonia is to the respiratory changes, but the cumulative data indicate that ammonia may contribute to transient respiratory distress in farmers working in enclosed livestock facilities.

A cross-sectional study of male workers at two fertilizer factories in Saudi Arabia showed a significant association between exposure to ammonia gas and respiratory symptoms including bronchial asthma (Ballal et al. 1998). Workers in factory one were exposed to air ammonia levels of 2.82–183.86 ppm (2.0–130.4 mg/m^3), and workers in factory two were exposed to 0.03–9.87 ppm (0.02–7.0 mg/m^3).

However, continuous exposure levels for workers could not be calculated because the number of days worked per week was not provided by the study authors. Logistic regression analysis showed that ammonia concentration was significantly related to cough, phlegm, wheezing (with and without shortness of breath), and asthma, whereas smoking was only a factor for wheezing and phlegm. Additionally, those workers exposed to ammonia levels above the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) of 25.4 ppm (18 mg/m^3) had significantly higher relative risks for cough, phlegm, wheezing, dyspnea, and asthma than workers exposed to levels below the TLV. Incidence of wheezing was also elevated in workers exposed to ammonia levels below the TLV. Cumulative ammonia concentration (CAC) of >50 mg/m^3-years also showed a significantly increased relative risk for all of the above symptoms compared to workers with a CAC of ≤50 mg/m^3-years. None of the relative risks for workers in the second factory (ammonia levels <25.4 ppm) were significant.

Other occupational studies also evaluated the effects of ammonia exposure and pulmonary function. Firefighters who reported exposure to ammonia while working had a rate of decline of FEV_1 of 1.7 times that of nonexposed firefighters over a period of 6–10 years (Tepper et al. 1991).

Children (8–9 years old) who attended two schools in the vicinity of a fertilizer plant had higher incidences of acute respiratory diseases than children of the same age who attended a school 20 kilometers away (Gomzi and Šarić 1997). Incidence was related to levels of measured pollutants (ammonia, hydrogen fluoride, nitrogen dioxide, total suspended particulate matter, and smoke) in the inside and outside air. Forced expiratory volumes were not statistically different between the three schools. These results indicate that exposure to low levels of ammonia (0.04–0.23 ppm) and other air-borne pollutants may not cause functional respiratory deficits, but may lower the resistance to respiratory pathogens in children. These effects may be due in part or in whole to toxicants other than ammonia, such as nitrogen dioxide.

Case reports of individuals acutely exposed to anhydrous or aqueous ammonia reported respiratory effects including nasal irritation; epiglottic, laryngeal, pharyngeal, tracheal, and pulmonary edema; dyspnea; wheezing; coughing; rhonchi; pneumonia; and cardio-respiratory arrest (de la Hoz et al. 1996; George et al. 2000; Kerstein et al. 2001; Latenser and Lucktong 2000; Leduc et al. 1992; Lee et al. 1993; Millea et al. 1989; Morgan 1997; Prudhomme et al. 1998; Weiser and Mackenroth 1989). de la Hoz et al. (1996) described the initial and residual effects of three adult males who had been acutely exposed to ammonia

gas in separate incidents. All three men complained of burning eyes, throat, and skin, cough, and wheezing, and all had been treated at hospitals shortly after exposure. Follow-up examinations 2–2½ years later showed persistent dyspnea, cough, and wheezing at rest and/or on exertion, which is consistent with restrictive lung disease secondary to acute ammonia inhalation injury. Another man exposed to anhydrous ammonia gas experienced pharyngeal and laryngeal edema, dyspnea, chest tightness, copious bronchial secretions, and wheezing (Leduc et al. 1992); 12 years postexposure, he continued to have cough, exertional dyspnea, and recurrent bronchial infections. Similar cases were reported by Kerstein et al. (2001) and Latenser and Lucktong (2000); no follow-up reports were available.

A more severe exposure was reported by George et al. (2000). An adult male was found unconscious next to a burst pipe carrying liquefied ammonia. He had ocular and cutaneous burns and severe difficulty breathing. Over the next 27 days, he suffered many medical setbacks, including attacks of bradycardia, a complete circulatory collapse from which he was resuscitated, and finally, a fatal cardiac arrest from severe bleeding. Another similar severe exposure resulted in the death of the patient 13 days postexposure due to treatment-resistant bronchopneumonia; histological examination showed massive, hemorrhagic pulmonary edema, regions of emphysema, and edema of the epiglottis and glottis (Weiser and Mackenroth 1989).

Reports of apparently rare effects have been found. A man exposed occupationally for 5 months to low levels of ammonia gas (8–15 ppm) from ammonia-containing silver polish developed asthma-like symptoms (Lee et al. 1993). Separate specific bronchial provocation tests to the silver polish and to 12 ppm ammonia produced asthmatic reactions, implicating the ammonia in the silver polish as the cause. Another study reported hyposmia (loss of the sense of smell) in a man following acute inhalation exposure (for several hours) to an unknown concentration of ammonia gas; the hyposmia had not resolved 30 months after exposure (Prudhomme et al. 1998).

Studies in animals have demonstrated similar dose-effect and duration-effect patterns for the respiratory tract. Acute exposures (1 hour to 1 week) to low concentrations of ammonia (≤1,000 ppm) irritate the upper respiratory tract whereas exposures (3 hours to 2 weeks) to high concentrations (≥4,000 ppm) result in severe damage to the upper and lower respiratory tract and alveolar capillaries (Coon et al. 1970; Kapeghian et al. 1982; Mayan and Merilan 1972; Richard et al. 1978a, 1978b; Schaerdel et al. 1983; Stombaugh et al. 1969). Prolonged or repeated exposures to lower levels (≥150 ppm) produce inflammation and lesions of the upper respiratory tract (Broderson et al. 1976; Coon et al. 1970).

Clinical and histological effects have been seen in the lungs of animals following exposure to ammonia gas (Dodd and Gross 1980; Gaafar et al. 1992; Sjöblom et al. 1999). Cats exposed to 1,000 ppm ammonia gas for 10 minutes and observed for up to 35 days showed a biphasic course of respiratory pathology (Dodd and Gross 1980). Effects seen at 24 hours post-exposure included severe dyspnea, anorexia, and dehydration, with rhonchi and coarse rales evident upon auscultation. Microscopy of lung samples on day 1 showed necrotizing bronchitis in the large conducting airways, and necrosis and sloughing of the epithelium and acute inflammatory reaction in the bronchi. On day 7, the mucosal lesions had resolved, but on day 35, varying degrees of bronchitis and early bronchopneumonia with areas of bulbous emphysema were seen. Gross pathology revealed varying degrees of congestion, hemorrhage, edema, interstitial emphysema, and collapse of the lungs at all time points. Pulmonary resistance was increased throughout the study (Dodd and Gross 1980). Swiss mice exposed to 909 ppm, but not 303 ppm, ammonia gas 6 hours/day, 5 days/week for 4–14 days had histological lesions in the respiratory epithelium in the nasal cavity (Zissu 1995); no lesions were observed in the trachea or lungs. Nasal mucosa was adversely affected in adult male mice exposed to vapor of 12% ammonia solution for 15 minutes/day, 6 days/week for 4, 5, 6, 7, or 8 weeks (Gaafar et al. 1992). Histological changes progressed from weeks 4–8 from crowding of cells forming crypts and irregular arrangements to epithelial hyperplasia, patches of squamous metaplasia, loss of cilia, and dysplasia of the nasal epithelium. One animal that had loss of polarity of the epithelium, hyperchromatism, and mitotic figures with an intact basement membrane also had a carcinoma *in situ* in one nostril. At week 8, one mouse had an invasive adenocarcinoma of the nasal mucosa. Histochemical results were also abnormal. The levels and cell locations of succinic dehydrogenase, acid phosphatase, alkaline phosphatase, and nonspecific esterase activities were altered, indicating altered cell metabolism and energy production, cell injury, proliferation, and possibly chronic inflammation and neoplastic transformation (Gaafar et al. 1992).

Anesthetized, mechanically ventilated rabbits exposed to high levels of nebulized ammonia (2 mL of 23–27% ammonia solution; estimated by the study authors as peak ammonia concentrations of 35,000–39,000 ppm) for 4 minutes had a decrease in blood oxygen saturation and an increase in airway pressure (a measure of changes in airway resistance) (Sjöblom et al. 1999). Arterial oxygen tension decreased from 23.3 (±3.6) to 11.0 (±3.6) kPa and peak airway pressure increased from 13 (±2) to 17 (±2) cm H_2O. At baseline and 5 and 15 minutes after ammonia administration, measurements were taken via a catheter in the left auricular artery, which monitored pressure and sampled for arterial blood gases, and via transducers in the ventilator. Thirty and 150 minutes after ammonia exposure, rabbits received inhalation therapy of either 0.5 mg budesonide (a steroid) or a placebo, and airway pressure, hemodynamics, and gas exchange were measured every 30 minutes for 6 hours. Slight, gradual

improvement of blood gas parameters was noted over the 6-hour observation period in all rabbits, with or without steroid treatment; however, no parameters approached normal during that time period.

Other studies examined pigs in normal swine production facilities (Donham 1991) or in environmentally regulated enclosures (Diekman et al. 1993; Gustin et al. 1994; Urbain et al. 1994). Donham (1991) investigated the correlation of housing air environment (in the finishing barn) to swine diseases and productivity over 12 months on 28 swine farms. Total dust, respirable dust, endotoxin activity of the dust, and hydrogen sulfide levels were determined, and area dust and microbial counts were monitored at 1.2 meters above the floor (the human breathing zone). Ammonia and carbon dioxide levels were determined 1.2 meters and 20 cm (swine breathing zone) above the floor. The average ammonia concentration in the human breathing zone for all farms was 9.1 ppm; the mean concentration in the swine breathing zone was 14.5 ppm. The mean concentrations of environmental contaminants were calculated for the most productive farrowing operations and the least productive ones and compared with lower production variables (Donham 1991). Ammonia concentration was related to number of pigs weaned per litter, and total and respirable dust concentrations were related to prolonged age to reach a weight of 25 kg. Another comparison involved the stratification of the finishing farms into quartiles according to percentage of pigs with specified disease conditions and comparison of mean concentrations of various environmental contaminants for each farm in each strata (Donham 1991). Levels of ammonia (in the animal breathing zone) greater than 25, 29, and 23 ppm were associated with buildings in which pneumonia, pleuritis, and arthritis, respectively, were greater than the mean value for the group. Overall, respirable dust (>0.8 mg/m^3), ammonia (>23 ppm in the animal breathing zone), and carbon dioxide (>2,000 ppm) levels were most often associated with increased disease. Possible study shortcomings noted by the study author were that pre-existing conditions could have been present in the pigs (before they entered the finishing barns) and that nasal turbinates were not routinely examined for abnormalities. These data suggest that ammonia may contribute to respiratory and other pathological conditions in pigs raised in crowded, enclosed conditions, but the exact contribution of ammonia is difficult to assess.

The lungs of young pigs exposed continuously to 0, 25, 50, or 100 ppm ammonia gas for 6 days in air-pollutant exposure chambers were removed, ventilated, and perfused, and the pulmonary vascular hemodynamics and permeability and the endotoxin-induced vascular response were assessed (Gustin et al. 1994). In lungs from pigs exposed to 100 ppm, but not 25 or 50 ppm ammonia, the endotoxin-induced vascular response seen in lungs from control pigs was abolished. The study authors suggested that this is due to a modification of the balance between vasodilators (such as cyclooxygenase products and platelet activating factor) and vasoconstrictors (such as prostacyclin). Since vasoconstriction, as induced by

endotoxin, may serve as a protective mechanism in the lungs and attenuate edema formation, the effective abolishment of this effect by ammonia may be detrimental.

Young pigs exposed continuously to ammonia vapors (0, 25, 50, or 100 ppm) for 6 days in air-pollutant exposure chambers had increased numbers of neutrophils in nasal lavage fluid in all exposure groups (Urbain et al. 1994) and increased porcine serum albumin at 100 ppm.

Not all studies have shown adverse respiratory effects from intermediate exposure to ammonia vapors. Groups of gilts (virgin female pigs) were raised from the age of 2–4.5 months in a conventional grower unit where they were naturally exposed to mycoplasmal and bacterial pathogens that cause enzootic pneumonia and atrophic rhinitis (Diekman et al. 1993). The pigs were then transferred to environmentally regulated rooms, where they were exposed continuously to low (mean 7 ppm) or moderate (mean 35 ppm) levels of ammonia for 6 weeks. No statistically significant differences were seen in the percent of lung tissue containing lesions or in snout grade (Diekman et al. 1993). Ninety-five percent of all gilts had lung lesions, with a wide range of degree of severity. Snouts were graded at the level of the second deciduous premolar as having normal turbinates (grade of 0), slight to moderate degeneration (grade of 1–3), or severe degeneration to complete loss of turbinates (grade of 4 or 5). Some of the gilts were continuously exposed through puberty and breeding (around 205 days of age) and the lungs and turbinates were examined at 30 days of gestation. No statistically significant differences were observed in percent of lung tissue containing lesions or in snout grade (Diekman et al. 1993).

A number of cattle were acutely exposed to anhydrous ammonia when a pipeline running through their pasture ruptured and leaked 1,800 barrels of ammonia in a short period of time (Morgan 1997). The ammonia combined with moisture and formed a white cloud (ammonia aerosol), which drifted south across two additional fields containing cattle. In the field where the rupture occurred, four head of cattle were found dead and two others were euthanized because of blindness and respiratory distress. Cattle in the adjacent pasture had runny eyes and noses and were coughing and wheezing. Eight days after the pipeline rupture, the cloud of ammona aerosol, which had apparently settled in a low-lying protected area, blew back up the valley and exposed the remaining cattle again and also exposed a horse in the same pasture. All animals had respiratory distress, elevated body temperatures, and one cow and the horse had swollen tongues and enlarged lymph glands. All cattle were given antibiotics and some were treated specifically for respiratory problems. No measurements or estimations of ammonia concentrations were provided and no follow-up examinations were available to assess long-term effects from the exposures.

All reliable LOAELs and highest NOAELs are presented in Table 3-1 and Figure 3-1.

Cardiovascular Effects. Acute exposure to highly concentrated aerosols of ammonium compounds may cause elevated pulse and blood pressure, bradycardia, and cardiac arrest in humans (George et al. 2000; Hatton et al. 1979; Montague and Macneil 1980; White 1971). These effects did not occur after acute exposure to 500 ppm ammonia or repeated exposure to 100 ppm ammonia (Ferguson et al. 1977; Silverman et al. 1949).

Cardiovascular changes that may be analogous to those observed in humans have been observed in rabbits exposed to high concentrations of ammonia (Richard et al. 1978b). Bradycardia was seen at 2,500 ppm, and hypertension and cardiac arrhythmias leading to cardiovascular collapse followed acute exposures to concentrations exceeding 5,000 ppm. Pathological correlates for these effects have not been demonstrated. Atrophy of pericardial fat has been observed in mice exposed to 4,000 ppm ammonia (Kapeghian et al. 1982). Myocardial fibrosis has been observed in rats, guinea pigs, rabbits, dogs, and monkeys after prolonged (90 days) continuous exposure to 653 ppm (Coon et al. 1970). The contribution of these lesions to the morbidity and mortality of affected animals has not been determined.

Exposure of pigs *in vivo* to up to 100 ppm ammonia for 6 days did not alter the baseline values of any hemodynamic or permeability parameters (arterial, pre- or postcapillary, or venous blood flow resistance, or total pulmonary blood flow resistance), but did eliminate the hemodynamic response to *Escherichia coli* endotoxins in the lungs (Gustin et al. 1994). This may affect the ability of the lungs to resist bacterial infection. The pulmonary blood flow resistance measurements were taken *in vitro* in ventilated and perfused lungs from pigs exposed to ammonia *in vivo* (Gustin et al. 1994). Reliable LOAELs and highest NOAELs for cardiovascular effects are presented in Table 3-1 and Figure 3-1.

Gastrointestinal Effects. Exposure to highly concentrated aerosols of ammonium compounds can produce burns of the lips, oral cavity, and pharynx, along with edema of these areas (Hatton et al. 1979; Kass et al. 1972; Leduc et al. 1992; Levy et al. 1964; Price et al. 1983; Stroud 1981; Ward et al. 1983; Yang et al. 1987). Gastrointestinal effects of ammonia in animals have not been reported. As shown in Table 3-1, pathological changes in the gastrointestinal tract were not observed in guinea pigs exposed repeatedly to 170 ppm ammonia (Weatherby 1952).

Hematological Effects. Cyanosis, elevated white blood cell count, and pulmonary artery thrombosis have been observed in humans exposed to highly concentrated aerosols of ammonium compounds (Sobonya 1977; Taplin et al. 1976; Voisin et al. 1970; Ward et al. 1983; White 1971).

Standard hematological measurements, including blood hemoglobin and differential cell counts, have been reported for a few animal species. As shown in Table 3-1 and Figure 3-1, acute hematological effects of ammonia have not been demonstrated (Doig and Willoughby 1971; Gustin et al. 1994). Pigs exposed to up to 100 ppm ammonia for 6 days had no statistically significant differences from controls in total leukocytes or percent lymphocytes, neutrophils, or eosinophils (Gustin et al. 1994). Repeated exposure to 1,100 ppm had no effect on hematological parameters in guinea pigs, rats, and rabbits (Coon et al. 1970). Weatherby (1952) reported increased concentrations of hemosiderin in the spleen of guinea pigs exposed to 170 ppm ammonia for 18 weeks. This suggests the possibility of increased turnover of red blood cells; however, this has not been corroborated.

Musculoskeletal Effects. Spasms of muscles of the extremities have resulted from an acute exposure of a man to anhydrous ammonia gas (White 1971), but this was probably caused by an effect of ammonia on the nervous system.

Hepatic Effects. Hemorrhagic necrosis of the liver was observed in an individual exposed to a lethal concentration of ammonia gas and liquid for a short period of time (<45 minutes) (Heifer 1971). No other cases of hepatic effects have been reported in humans. Hepatic effects are usually not seen in animals exposed to ammonia gas. As shown in Table 3-1, liver necrosis has been observed following acute lethal exposure of mice to 3,440 ppm ammonia for 1 hour (Kapeghian et al. 1982). Fatty changes of liver plate cells were seen in rats following continuous long-term exposure to 642 ppm ammonia for 90 days, but no such changes were seen in rats, squirrel monkeys, and guinea pigs exposed to 1,086 ppm ammonia 8 hours/day, 5 days/week for 6 weeks (Coon et al. 1970).

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to ammonia. In animals, renal effects do not appear to be an important feature of the toxicity of inhaled ammonia. Effects reported have not been corroborated or cannot be interpreted. Mild abnormalities in the renal tubules have been described in guinea pigs exposed to 170 ppm for 12 weeks, 5 days/week, 6 hours/day; however, renal effects at this relatively low level have not been corroborated (Weatherby 1952). Exposure to more than 6 times this concentration for 6 weeks, 5 days/week, 8 hours/day did not

result in pathological changes to the kidney (Coon et al. 1970). Renal tubular calcification (severity not reported) has been reported in rats continuously exposed to near lethal levels (Coon et al. 1970).

Endocrine Effects. Adrenaline levels in urine, 17-oxycorticosteroids in the urine, and 11-oxycorticosteroid levels in blood were increased in humans exposed to 3.0 ppm ammonia for 37 days (Kalandarov et al. 1984). Exposure to 7.2 ppm for 17 days also increased adrenaline levels in urine and 17-oxycorticosteroids in the urine, and increased free, but not total, 11-oxycorticosteroid levels in blood (Kalandarov et al. 1984). Experimental details were lacking in this study; additionally, no clinical or histological data were provided for this or other end points in this study and no supporting data are available in the literature. Therefore, the significance of these effects is unclear. Exposure of pigs to up to 100 ppm ammonia for 6 days did not significantly alter the plasma cortisol concentration (Gustin et al. 1994). No statistically significant difference was seen in adrenal gland weight of female pigs exposed to about 35 ppm ammonia for 6 weeks or for 6 weeks plus through day 30 of gestation compared to pigs exposed for similar time frames to about 7 ppm ammonia (Diekman et al. 1993). No unexposed controls were included in that study. The endocrine system does not appear to be a primary target of inhaled ammonia.

Dermal Effects. Ammonia gas and aerosols of ammonium compounds derived from anhydrous ammonia are dermal irritants in humans and animals. These effects are described in the discussion of dermal effects associated with dermal exposure (Section 3.2.3.2).

Ocular Effects. Ammonia gas and aerosols of ammonium compounds derived from anhydrous ammonia are ocular irritants in humans and animals. These effects are described in the discussion of ocular effects associated with dermal exposure (Section 3.2.3.2).

Body Weight Effects. Reduced body weight has been observed in rats exposed via inhalation to 500 ppm (Richard et al. 1978a) and in pigs exposed to 50 ppm or more ammonia for 6 days (Gustin et al. 1994; Urbain et al. 1994). Pigs gained less weight and showed decreased food consumption when exposed to 100 ppm ammonia for 4 or 5 weeks (Drummond et al. 1980; Stombaugh et al. 1969). Female pigs exposed to about 35 ppm for 6 weeks gained less weight than those exposed to only about 7 ppm (Diekman et al. 1993). However, females that were continuously exposed to about 7 or 35 ppm ammonia from 6 weeks before breeding until day 30 of gestation had no statistically significant difference in body weight (Diekman et al. 1993); however, no controls were included in this study.

3.2.1.3 Immunological and Lymphoreticular Effects

Several case reports describe occupational asthma that developed due to exposure to aerosols that contained ammonium compounds (Ballal et al. 1998; Lee et al. 1993; Weir et al. 1989).

Secondary infections often complicate the clinical outcome of burns and respiratory lesions related to exposure to highly concentrated aerosols derived from anhydrous ammonia (Sobonya 1977; Taplin et al. 1976). However, there is no evidence that the decreased immunological resistance represents a primary impairment of the immune system in humans following exposure to ammonia. Nevertheless, as shown in Table 3-1 and Figure 3-1, studies in animals have shown that acute and long-term exposure to ammonia can decrease the resistance to bacterial infection and decrease immune response to infection. A significant increase in mortality was observed in mice exposed to ammonia for 168 hours followed by exposure to the LD_{50} of *Pasteurella multocida* (Richard et al. 1978a). Exposure of rats to ammonia at ≥25 ppm for 4–6 weeks following inoculation with *Mycoplasma pulmonis* intranasally significantly increased the severity of respiratory signs characteristic of murine respiratory mycoplasmosis (Broderson et al. 1976). Guinea pigs exposed to 90 ppm ammonia for 3 weeks developed a significant decrease in the cell-mediated immune response to challenge with a derivative of tuberculin (Targowski et al. 1984). Furthermore, the response of blood and bronchial lymphocytes to mitogens (phytohemagglutinin, concanavalin A, purified protein derivative of tuberculin) was markedly reduced. The hemodynamic response (increased total pulmonary blood flow resistance) to *E. coli* endotoxins in the lungs of pigs was eliminated by exposure to up to 100 ppm ammonia for 6 days, which may affect the ability of the lungs to resist bacterial infection (Gustin et al. 1994). Also, a reduction in gamma globulin concentration was reported in pigs exposed to 100 ppm ammonia for 31–45 days (Neumann et al. 1987).

3.2.1.4 Neurological Effects

Case reports of accident victims exposed to highly concentrated aerosols derived from anhydrous ammonia describe blurred vision, diffuse nonspecific encephalopathy, loss of consciousness, muscle weakness, and decreased deep tendon reflexes (George et al. 2000; Hatton et al. 1979; Latenser and Lucktong 2000; White 1971). Acute exposure to low levels of ammonia (100 ppm) has been shown to depress free-access wheel running behavior in rodents (Tepper et al. 1985). No overt symptoms of neurological disorders were reported in guinea pigs or monkeys that were exposed to up to 1,105 ppm ammonia for 6 weeks (Coon et al. 1970). Exposure of the nasal mucosa to ammonia-saturated air elicited vasodilatation and corresponding increased blood flow and reflex hypertension in the lower lip of cats

(Izumi and Karita 1993). Stimulation of the nasal mucosa by chemical irritants has been shown to elicit changes in the respiratory system, such as apnea, laryngeal spasm, and bronchoconstriction, and in the cardiovascular system, such as bradycardia and variable blood pressure changes (Izumi and Karita 1993). Brain glutamine levels have also been shown to increase in rats that inhaled 25 or 300 ppm ammonia vapor for 6 hours/day for 5 days, which is likely a result of ammonia metabolism by the astrocytic glutamate-glutamine cycle (Manninen and Savolainen 1989; Manninen et al. 1988).

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to ammonia. No statistically significant differences were noted in ovarian or uterine weights of pigs exposed to about 7 or 35 ppm ammonia for 6 weeks (Diekman et al. 1993). Female pigs that were continuously exposed to about 35 ppm ammonia from 6 weeks before breeding until day 30 of gestation had no statistically significant differences in age at puberty, number of live fetuses, or fetus-to-corpus luteum ratio compared to pigs exposed to only about 7 ppm (Diekman et al. 1993). No unexposed controls were included in that study.

3.2.1.6 Developmental Effects

No information was located regarding developmental effects of ammonia in humans following inhalation exposure. No statistically significant difference in fetal length was evident at 30 days of gestation in offspring of pig dams that were continuously exposed to about 7 or 35 ppm ammonia from 6 weeks before breeding until day 30 of gestation (Diekman et al. 1993).

3.2.1.7 Cancer

Carcinogenic potential of ammonia by the inhalation route has not been assessed in humans or animals. One case report was found of an individual who developed epidermal carcinoma of the nasal septum 6 months after being badly burned by accidental contact with a refrigeration ammonia-oil mixture (Shimkin et al. 1954). However, the role of ammonia is impossible to ascertain and no conclusion can be drawn from this study. Shimkin et al. (1954) indicated that “no single case can prove a general principle, and it is only by the publication of additional reports of similar cases that enough data can become available for critical analysis.” No other such reports were located, although other cases of inhalation

exposure to ammonia from spills have been followed for more than 6 months after exposure. One of 10 adult male mice exposed to ammonia gas for 15 minutes/day 6 days/week for 8 weeks had mitotic figures with an intact basement membrane and a carcinoma *in situ* in one nostril and one mouse had an invasive adenocarcinoma of the nasal mucosa (Gaafar et al. 1992). Again, there is no conclusive evidence that ammonia played a role in the induction of the carcinoma. Gaafar et al. (1992) provided an alternate explanation by stating that "prolonged exposure to ammonia may interfere with the normal protective reflexes of the respiratory nasal mucosa resulting in the accumulation of particulate matter initiating or promoting a neoplastic process." However, the plausibility of tumor formation in only 8 weeks by a weak carcinogen such as particulate matter is debatable.

3.2.2 Oral Exposure

As discussed in Chapter 4, ammonia in aqueous solution exists in equilibrium with ammonium hydroxide, a weak base, which is partially ionized in water. Degree of ionization is dependent on pH; at physiological pH, ammonium hydroxide is 99% ionized, but at pH 9.25, is only 50% ionized. Information available for humans exposed to ammonia by the oral route usually involved case reports of people who swallowed household ammonia (ammonium hydroxide). Studies by the oral route in animals generally have used ammonium salts or ammonium hydroxide. For these reasons, oral doses are expressed as mg NH_4^+/kg/day, given as the particular ammonium compound.

In many animal studies, the animals were administered ammonium chloride. Ammonium chloride is commonly used to induce metabolic acidosis in experimental animals. The acidosis is due to the formation of hydrogen ions from the metabolism of ammonium ions to urea. WHO (1986) notes that the ingestion of ammonium chloride in doses around 500–1,000 mg/kg/day for 1–8 days (longer treatment would worsen the condition) has induced metabolic acidosis in mice, guinea pigs, rats, rabbits, and dogs. Metabolic acidosis can result in a variety of nonspecific changes in neurological, cardiovascular, pulmonary, gastrointestinal, and musculoskeletal function, as well as in changes in hematological and clinical chemistry parameters.

3.2.2.1 Death

Human deaths due to ingestion of household ammonium salts have been reported (Klein et al. 1985; Klendshoj and Rejent 1966), but no quantitative data for oral exposure in humans were located. A

69-year-old woman who ingested an unknown quantity of lemon ammonia (3% ammonium ion) was found semi-conscious and making gurgling respiratory sounds (Klein et al. 1985). Radiographic results were consistent with aspiration pneumonia, and endoscopy showed laryngeal and epiglottic edema and a friable, erythematous esophagus with severe corrosive injury. The woman died several days later after developing acute respiratory distress syndrome and renal failure (Klein et al. 1985). A 57-year-old man was found dead with a glass containing dilute ammonium hydroxide (2.4% ammonium ion) nearby (Klendshoj and Rejent 1966); autopsy showed hemorrhagic esophagus, stomach, and duodenum. As shown in Table 3-2 and Figure 3-2, 303 mg ammonium/kg as ammonium chloride is a lethal dose in guinea pigs when given as single gavage dose (30/40 died) (Koenig and Koenig 1949). Death, in this study, resulted from pulmonary edema. No deaths were seen in cats, rabbits, guinea pigs, or rats after a similar dose of ammonium (337 mg ammonium/kg given as ammonium chloride) (Boyd and Seymour 1946).

3.2.2.2 Systemic Effects

No information was located regarding dermal or ocular effects of ammonia or ammonium compounds in humans or animals following oral exposure.

Respiratory Effects. No information was located regarding respiratory effects of ammonia or ammonium compounds in humans following oral exposure. Guinea pigs that received a single gavage dose of ammonium chloride developed serious respiratory effects including increased rate and depth of respiration, pulmonary edema, and death by respiratory failure (Koenig and Koenig 1949). Because the blood pH of the guinea pigs decreased after administration of ammonium chloride, adjustments in respiratory rate and depth may have been a compensatory mechanism for acidosis. Similarly, administration of ammonium chloride in doses of approximately 100 mg of NH_4^+/kg/day (as ammonium chloride) or higher for up to a year to rabbits resulted in metabolic acidosis and compensatory changes in respiratory rate and tidal volume (Seegal 1927). The low blood pH results in increased lung ventilation, which increases the elimination of carbon dioxide from the blood, and therefore, can be considered a compensatory response to acidosis rather than a direct effect of ammonium ion on the lungs or respiratory system.

Cardiovascular Effects. No information was located regarding cardiovascular effects of ammonia or ammonium compounds in humans following oral exposure. No pathological abnormalities were noted in the hearts of adult and weanling rats fed doses of up to 79 mg ammonium/kg/day as ammonium

Table 3-2 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
	ACUTE EXPOSURE								
	Death								
1	Gn Pig	1 d					286	(death due to pulmonary edema)	Koenig & Koenig 1949 NH4CL
	Systemic								
2	Rat (Sprague-Dawley)	6 d (W)	Hemato		2325	(elevated serum calcium)			Barzel 1975 NH4Cl
3	Rat (Wistar)	3 or 7 d (F)	Bd Wt	22 F	3150.4 F	(10% reduction in final body weight)			Bodega et al. 1993 ammonium acetate
4	Rat (Wistar)	3 or 7 d (F)	Bd Wt	22	3102.2	(final body weight decreased by 15%)			Boyano-Adanez et al. 1996 ammonium acetate
5	Rat (Sprague-Dawley)	7 d Gavage - NS	Renal		433	(renal enlargement due to cell hypertrophy)			Janicki 1970 NH4Cl
6	Gn Pig	1 d Gavage - NS	Resp				303	(pulmonary edema)	Koenig & Koenig 1949 NH4CL

Table 3-2 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Neurological						
7	Rat (Wistar)	3 or 7 d (F)		22	3102.2 (decreased binding of somatostatin to receptors in frontoparietal cortex and hippocampus)		Boyano-Adanez et al. 1996 ammonium acetate
	INTERMEDIATE EXPOSURE						
	Systemic						
8	Rat	330 d (W)	Musc/skel		991 (reduced calcium less fat-free solid)		Barzel & Jowsey 1969 NH4Cl
			Bd Wt		991 (reduced body weight)		
9	Rat (Wistar)	90 d (F)	Bd Wt	22 F	3150 F (15% reduction in final body weight after 90 days)		Bodega et al. 1993 ammonium acetate
10	Rat (Wistar)	15 d (F)	Bd Wt	22	3102.2 (final body weight gain decreased by 10%)		Boyano-Adanez et al. 1996 ammonium acetate
11	Rat	3 wk (W)	Renal	412			Freedman & Beeson 1961 NH4CL

Table 3-2 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
12	Rat (albino)	90 d 6 d/wk (W)	Cardio	79 F			Gupta et al. 1979 NH4NH2SO3
			Gastro	79 F			
			Hemato	79 F			
			Hepatic	79 F			
			Renal	79 F			
			Bd Wt	39.5 F	79 F (body weight decreased by 16%)		
13	Dog	11 wk Gavage - NS	Musc/skel			337 (bone deformity and softening)	Bodansky et al. 1932 NH4Cl
	Neurological						
14	Rat (Wistar)	15 d (F)		22	3102.2 (decreased binding of somatostatin to receptors in frontoparietal cortex and hippocampus)		Boyano-Adanez et al. 1996 ammonium acetate

Table 3-2 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)	
	Developmental							
15	Rat (Wistar)	Gd 1-ppd 21 (F)				4293	(BW decreased by 16-27%; decreased NMDA receptor function in neurons)	Minana et al. 1995 NH3CH3CO2

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

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); DW = drinking water; (F)= feed; F = female; Gd = gestation day; G = gavage; gastro = gastrointestinal; hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level;min = minute(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; NS = not specified; wk = week(s)

Figure 3-2. Levels of Significant Exposure to Ammonia And Ammonium Compounds - Oral

Acute (≤14 days)

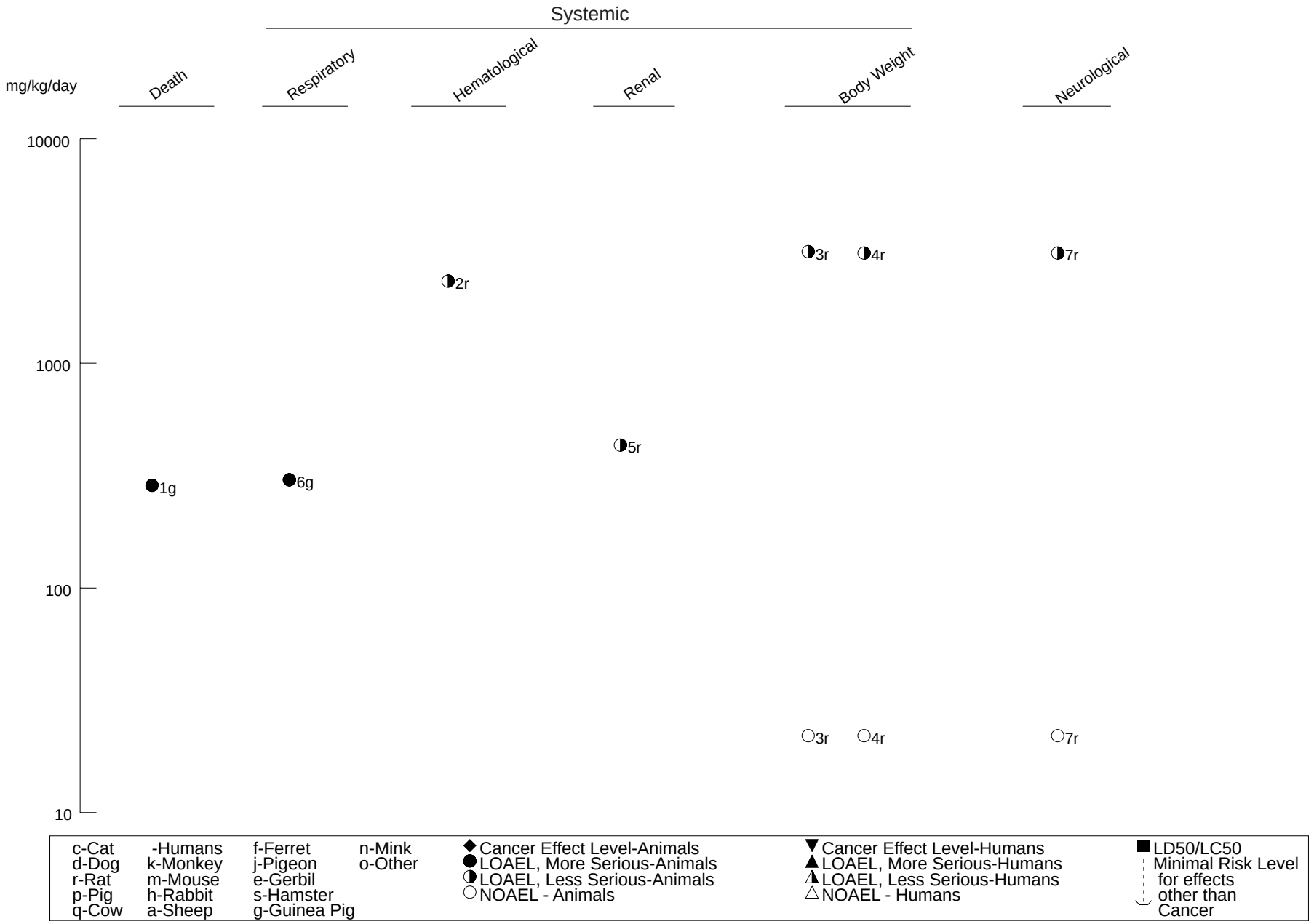
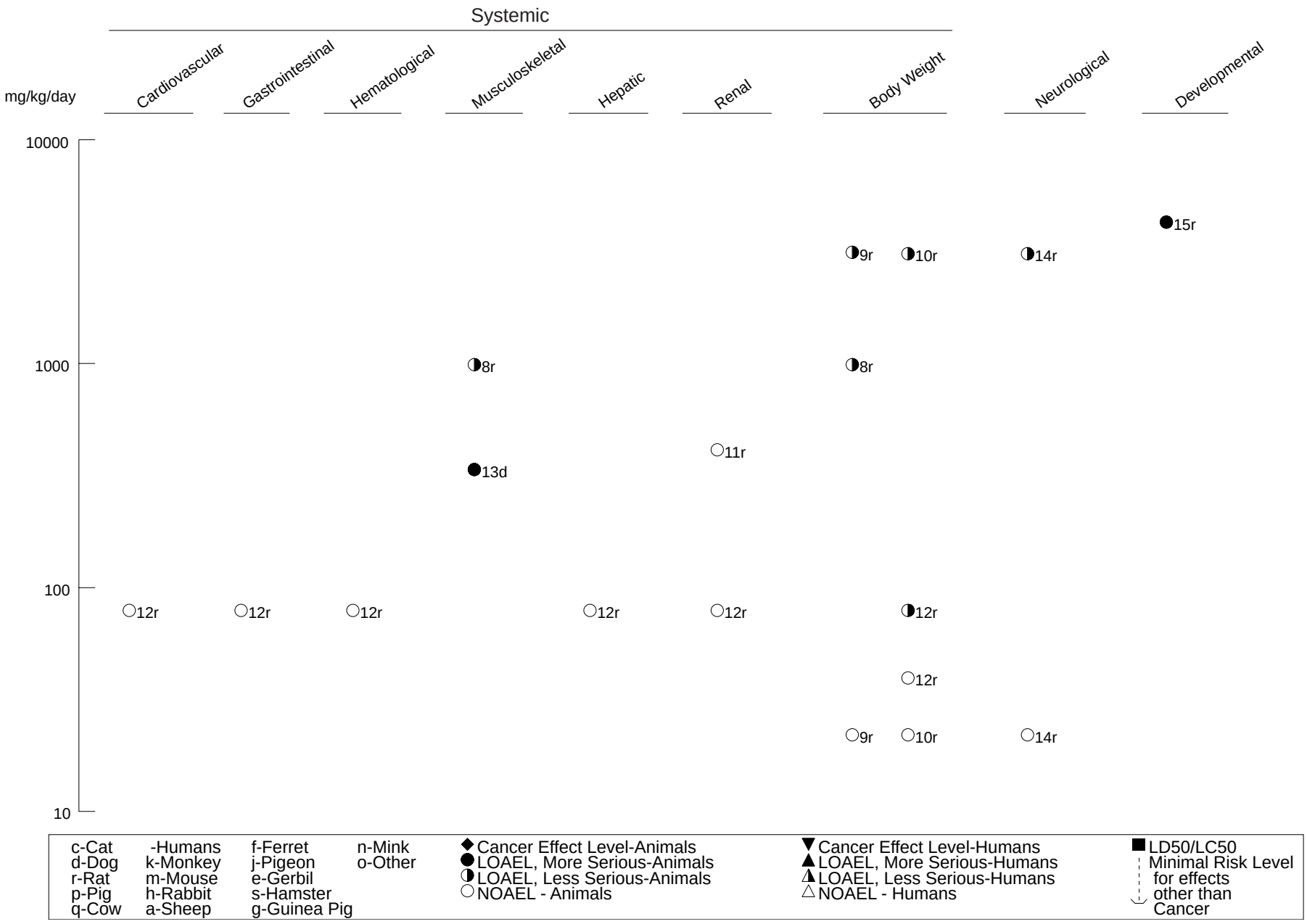


Figure 3-2. Levels of Significant Exposure to Ammonia And Ammonium Compounds - Oral (*Continued*)

Intermediate (15-364 days)



sulfamate for 90 days in drinking water (Gupta et al. 1979). These data are presented in Table 3-2 and Figure 3-2.

Gastrointestinal Effects. Several cases have been described of young children (2–3 years old) who bit into ammonia pellets/capsules (Lopez et al. 1988; Rosenbaum et al. 1998). Two of the children drooled and had ulcerative lesions on the tongue and/or on the buccal mucosa; one child had superficial ulcerations on the posterior esophageal wall and the other child had edematous, erythematous upper and lower lips with areas of desquamation, eschar of the hard palate, and edema and erythema of the supraglottic structures and upper trachea (Rosenbaum et al. 1998). All of the children experienced one or more of the following symptoms: vomiting, drooling, dysphagia, cough, or oral or pharyngeal burns (Lopez et al. 1988; Rosenbaum et al. 1998). None of the children had esophageal or respiratory burns and all healed within a few days. Esophageal lesions and edema were reported in five persons who ingested household ammonia (ammonium hydroxide), one of whom experienced acute respiratory obstruction (Christesen 1995; Klein et al. 1985). These observations were not quantified. The effects are probably due to the alkaline nature of ammonium hydroxide. A single case report described a self-administered ammonia solution enema that resulted clinically in anal pain, diffuse abdominal colic, and tenesmus (da Fonseca et al. 1998). Sigmoidoscopy showed diffuse erythematous friable mucosa with large ulcerations covered by yellowish exudate that receded in a few days, but chronic inflammation and fibrosis of the rectum and sigmoid colon was noted 3 months postexposure (da Fonseca et al. 1998).

No histopathological abnormalities of the gastrointestinal tract were observed in adult or weanling rats administered doses of up to 79 mg ammonium/kg/day as ammonium sulfamate for 90 days via drinking water (Gupta et al. 1979). Likewise, a 3% solution of ammonium chloride administered to rats via gastric tube produced no gastric mucosal damage in 1 hour and a 10% solution produced only a minimum of hemorrhagic lesions (about 9 mm^2) (Takeuchi et al. 1995). However, similar administration of 1 or 3% ammonium hydroxide in rats produced severe hemorrhagic lesions (about 26.6 or 97.7 mm^2, respectively) (Takeuchi et al. 1995). Gavage administration in rats of 0.3% ammonia (33.3 mg/kg) produced gastric mucosal lesions within 5 minutes with corresponding decreases in gastric wall immunoreactive endothelin-1 (ET-1) and immunoreactive thyrotropin-releasing hormone (TRH) concentrations and increases in gastric juice ET-1 and TRH concentrations (Mori et al. 1998). *In situ* gastric exposure has also shown ammonia-induced gastric mucosal damage (Murakami et al. 1995; Nagy et al. 1996). These lesions are exacerbated by neutrophil products, especially hypochlorous acid (Murakami et al. 1995) and cysteine proteases, such as some of the cathepsins (Nagy et al. 1996). Administration of 0.01% ammonia in drinking water to rats (approximately 42 mg/kg/day) for 8 weeks resulted in acceleration of cell

migration leading to mucosal atrophy in the stomach antrum, increased labeling indices, and enlargement of the proliferative zone in the antral and body mucosa (Tsujii et al. 1993).

Hematological Effects. No information was located regarding the hematological effects of ammonia or ammonium compounds in humans following oral exposure. Repeated exposure to ammonium chloride in animals resulted in metabolic acidosis with related changes in bone metabolism and serum calcium. For example, rats fed diets containing high levels of ammonium chloride had increased serum calcium (Barzel 1975). The increased serum calcium resulted from enhanced demineralization of bone in response to chronic acidosis. This effect was not found to be a specific effect of ammonium and was reported to occur in states of chronic metabolic acidosis produced from repeated doses of acidifying agents (e.g., hydrochloric acid, sulfuric acid). Decreased blood pH was seen in cats fed an acidifying diet containing ammonium chloride for several weeks (Kienzle and Wilms-Eilers 1994). As shown in Table 3-2 and Figure 3-2, no effects on blood hemoglobin or blood cell counts were observed in adult or weanling rats that received doses of up to 79 mg ammonium/kg/day administered as ammonium sulfamate in drinking water (Gupta et al. 1979).

Musculoskeletal Effects. No information was located regarding musculoskeletal effects of ammonia or ammonium compounds in humans following oral exposure. Guinea pigs and rats that received lethal gavage doses of ammonium chloride developed muscle weakness, fasciculation, and incoordination (Koenig and Koenig 1949). In other animal studies, repeated ingestion of ammonium salts resulted in metabolic acidosis, which stimulated bone demineralization. As is shown in Table 3-2 and Figure 3-2, repeated ingestion of ammonium chloride in drinking water resulted in net bone resorption in rats and bone deformities in dogs (Barzel and Jowsey 1969; Bodansky et al. 1932). This effect can be anticipated with repeated exposure to any acidifying agent.

Hepatic Effects. No information was located regarding hepatic effects of ammonia or ammonium compounds in humans following oral exposure. As shown in Table 3-2 and Figure 3-2, no toxic effects were noted in livers of adult or weanling rats fed doses of up to 79 mg ammonium/kg/day as ammonium sulfamate for 90 days in drinking water (Gupta et al. 1979).

Renal Effects. Renal failure was identified as the cause of death in humans after ingestion of an unknown amount of household ammonia (ammonium hydroxide) (Klein et al. 1985). It is not certain if this represents a primary effect of ammonium or is secondary to massive burns to the gastrointestinal tract.

Renal effects have been observed in animals following repeated oral doses of ammonium chloride. These effects may be secondary to chronic acidosis produced from the interaction of ammonium chloride with water (which results in an increased H^+ concentration) rather than from a direct effect of ammonium ion on the kidney. Renal enlargement, increased blood ammonia content, and increased urinary ammonia have been reported in rats exposed to 180–433 mg/kg/day for 3–7 days (Benyajati and Goldstein 1975; Janicki 1970; Lotspeich 1965;), but are unlikely to be indicative of renal pathology. The highest NOAELs and LOAELs are presented in Table 3-2 and Figure 3-2.

Endocrine Effects. No information was located regarding endocrine effects of ammonia or ammonium compounds in humans following oral exposure. Enlarged adrenal glands were observed in rabbits that received 124 mg ammonium/kg/day as ammonium hydroxide by gavage in water for 17 months (Fazikas 1939). These limited data suggest that the endocrine system is not a primary target for ammonia or ammonium compounds.

Body Weight Effects. Decreased body weight or weight gain has been observed in animals following oral exposure to ammonium ion (Barzel and Jowsey 1969; Bodega et al. 1993; Boyano-Adánez et al. 1996; Gupta et al. 1979; Noda and Chikamori 1976). Rats exposed to ammonium ion *in utero* and during lactation (dams received 4,293 mg ammonium/kg/day in the diet from gestational day 1 through lactation day 21) and then received a normal diet had showed reduced body weight gain (Miñana et al. 1995); body weight gain was reduced by 25 and 16% in male and female offspring, respectively, at 120 days of age. Rats that were continued on the same ammonia diet as their dams had an even greater reduction in body weight gain (27 and 26% for males and females, respectively) (Miñana et al. 1995). Birth weights were not reported in the Miñana et al. (1995) study. Gupta et al. (1979) noted increased water intake and reduced food intake in weanling rats, and decreased body weight in adults but not weanlings fed 79 mg ammonium/kg/day in drinking water for 90 days as ammonium sulfamate. This represents the LOAEL for this effect. A NOAEL of 39.5 mg ammonium/kg/day was also identified in this study (see Table 3-2 and Figure 3-2).

3.2.2.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological effects of ammonia or ammonium compounds in humans or animals after oral exposure.

3.2.2.4 Neurological Effects

No information was located regarding neurological effects of ammonia or ammonium compounds in humans after oral exposure.

Guinea pigs that received lethal gavage doses of ammonium chloride (303.5–404.7 mg NH_4^+/kg) developed neuromuscular effects including fasciculation; incoordination; hyperexcitability to tactile, auditory, and painful stimuli; and tonic convulsions (Koenig and Koenig 1949).

A number of studies have indicated that increased ammonium ion levels in the brain may disrupt energy production and modify the availability of some receptors that are involved in neurotransmission. Administration of 20% ammonium acetate in the diet of rats for 20 days resulted in statistically significant increases in brain ammonium ion (12.8-fold), glutamine (37%), and alanine (93%) and in some TCA cycle-associated components in the brain including glucose, lactate, and pyruvate, and decreases in brain cytosolic NAD^+/NADH ratio, β-hydroxybutarate, and ATP content (Kosenko et al. 1993). Rats with high NH_4^+ intake from administration of 20% ammonium acetate in the diet and 5 mM ammonium acetate in the water for up to 15 days had a decreased number of available somatostatin receptors in the frontoparietal cortex and hippocampus (Boyano-Adánez et al. 1996). Since somatostatin hyperpolarizes neurons in the cerebral cortex, the study authors speculated that this reduction in available receptors may contribute to the alteration of electrophysiological properties of neural tissue caused by excess NH_4^+ (Boyano-Adánez et al. 1996). Binding of [H^3]MK-801 (an NMDA receptor antagonist) to NMDA receptors was reduced by approximately 60% in cerebellar cell cultures from 8-day-old rats exposed to NH_4^+ *in utero* and during lactation (dams received 4,293 mg ammonium/kg/day in the diet from gestational day 1 through lactation day 8) (Miñana et al. 1995). Additionally, aspartate aminotransferase (AST) induction was absent in treated neurons (occurred in neurons from control rats), which also indicates impairment of NMDA receptors. Treated neurons were much more resistant to the toxic effects of glutamate than control neurons; since glutamate toxicity is mediated by NMDA receptors, attenuation of glutamate toxicity is indicative of impaired NMDA receptor function (Miñana et al. 1995). Loss of glial fibrillary acidic protein (GFAP) has been shown to occur in human spontaneous hyperammonemia (Kimura and Budka 1986; Kretzschmar et al. 1985; Sobel et al. 1981) and in other hyperammonemia models, such as portacaval shunt rats (Bodega et al. 1991; Suárez et al. 1992), but was not evident after exposure of rats to ammonium acetate (20% ammonium acetate in the diet and 5 mM ammonium acetate in the water for up to 90 days) (Bodega et al. 1993). Rats fed 19.5% ammonium acetate in the diet had increased NH_4^+ levels in the brain and altered assembly and disassembly of tubulin, an essential

component of the axonal transport system in the brain (Miñana et al. 1989a). The amount of polymerized tubulin increased but the amount of free tubulin was not affected. *In vitro* experiments using brains of rats fed a diet high in NH_4^+ indicated that the cause of the alteration might be a modification of the tubulin (and not the microtubule-associated proteins [MAPs], which modulate polymerization of the tubulin), which may result in a disruption in neurotransmission (Miñana et al. 1989a). Additional studies in rats brain showed that tubulin was significantly increased specifically in the septum, ventral hippocampus, dorsal hippocampus, hypothalamus, reticular formation, and frontal cortex, but not in the temporal amigdala, mammillary nucleus, locus coeruleus, caudate nucleus, or cingulate cortex after 2 months on the high ammonia diet (Miñana et al. 1989b).

3.2.2.5 Reproductive Effects

No information was located regarding reproductive effects of ammonia or ammonium compounds in humans or animals following oral exposure.

3.2.2.6 Developmental Effects

No information was located regarding the developmental effects of ammonia or ammonium compounds in humans. Rats exposed to NH_4^+ *in utero* and during lactation (dams received 4,293 mg ammonium/kg/day in the diet from gestational day 1 through lactation day 21), which then received a normal diet, had a statistically significant reduction in body weight gain (Miñana et al. 1995); body weight was reduced by 25 and 16% in male and female offspring, respectively, at 120 days of age. Rats that were continued on the same ammonia diet as their dams had an even greater decrease in body weight gain (27 and 26% for males and females, respectively) at 120 days of age (Miñana et al. 1995). No information was provided in the study regarding the health of the dams, but it is likely that the high ammonium dietary concentration made them hyperammonemic. Body weights and food consumption by the dams throughout the study were not reported.

3.2.2.7 Cancer

No information was located regarding carcinogenic effects of ammonia or ammonium compounds in humans following oral exposure. Exposure of mice to 193 mg ammonium/kg/day as ammonium hydroxide in drinking water for 2 years did not produce carcinogenic effects, nor did it affect spontaneous

development of breast cancer, which is common to C3H female mice (Toth 1972). No evidence of a carcinogenic effect was found in mice treated by gavage with ammonia dissolved in water alone at a dose of 42 mg NH_4^+/kg/day for 4 weeks or with diethyl pyrocarbonate alone, but 9 of 16 mice treated with a combination of ammonium and pyrocarbonate developed lung tumors (Uzvolgyi and Bojan 1980). The ammonia and pyrocarbonate may have reacted *in vivo* to form the carcinogen, urethane. In a group of mice treated with urethane, the incidence of lung tumors was 9 of 9. Data from studies *in vitro* cited by Uzvolgyi and Bojan (1980) demonstrated the formation of urethane from diethyl pyrocarbonate added to beverages containing ammonia. No lung tumors were observed in the offspring of mice exposed similarly to NH_4^+ and diethyl pyrocarbonate during pregnancy or during lactation (Uzvolgyi and Bojan 1985). In another study, Tsujii et al. (1992a, 1995) tested the hypothesis that ammonia produced in the stomach in humans infected with *Helicobacter pylori* may play a role in the development of gastric cancer. Rats pretreated with the initiator N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in the drinking water for 24 weeks before receiving 0.01% ammonia solution in the drinking water for 24 weeks had a statistically significantly greater incidence of gastric cancer (70% of rats) and number of tumors per tumor-bearing rat (2.1) than rats receiving only MNNG and tap water (31% and 1.3 tumors/rat) (Tsujii et al. 1992a). Additionally, the size, depth, and metastasis of the MNNG-initiated tumors were enhanced in the rats treated with ammonia (Tjusii et al. 1995). It can be estimated that the dose of ammonia received by the rats was approximately 42 mg/kg/day (the daily intake from food and water for the general population is approximately 0.3 mg/kg/day [WHO 1986]). The relevance of these studies to assess the cancer risk of oral exposure to ammonia is uncertain.

3.2.3 Dermal Exposure

Dermal exposure to ammonia may also result in some inhalation exposure. Therefore, based on the available data, it is not always clear to what extent each route of exposure contributes to the toxicity observed in dermal exposure studies.

3.2.3.1 Death

Human and animal deaths involving dermal exposure to ammonia and ammonium have been reported (Prokop'eva et al. 1973; Slot 1938; Sobonya 1977), but the extent of exposure is not known, and effects were probably due to inhalation exposure as well. A 25-year-old woman exposed to ammonia gas from a broken pipe had burns on her face, arms, and torso, and had difficulty breathing and swallowing (Slot

1938). She was treated symptomatically and with supportive treatment, but died about a month after exposure (Slot 1938). Autopsy showed edematous, inflamed, hemorrhagic epiglottis, trachea, and lungs. Petechial hemorrhages were found on the heart and the kidneys were congested with hemorrhagic nephritis. A 25-year-old man died after a tank of anhydrous ammonia exploded near him while he was farming (Sobonya 1977). Immediately after exposure he had mild bilateral conjunctival edema, burns over about 30% of his body surface, bilateral pulmonary edema, and severe respiratory distress. He developed pneumonia and died on the sixtieth day post-exposure. In rats, LC_{50} values of 112, 71.9, and 48.4 mg ammonia/L were determined for exposures of 15, 30, and 60 minutes, respectively (Prokop'eva et al. 1973). These data are presented in Table 3-3.

3.2.3.2 Systemic Effects

No information was located on hematological, musculoskeletal, hepatic, endocrine, or body weight effects in humans or animals after dermal exposure to ammonia or ammonium.

Dermal or multiple route exposure to ammonia or ammonium has produced respiratory, cardiovascular, gastrointestinal, renal, dermal, and ocular effects.

Respiratory Effects. Respiratory effects have been reported in humans from exposure to massive amounts of ammonia gas, but no quantitative data were located. It is also unclear as to what extent the effects were a result of inhalation and dermal exposure. Tracheitis, bronchitis, edema, and bronchopneumonia were reported by Slot (1938). Lung infection and respiratory distress were reported in one case (Sobonya 1977). Dyspnea, rales, rhonchi, and blocked airways were found by Levy et al. (1964). The effects probably resulted from concurrent inhalation and dermal exposure. No information was located regarding respiratory effects of ammonia or ammonium in animals following dermal or ocular exposure.

Cardiovascular Effects. Elevated pulse, shock, and cardiac failure were reported in humans from accidental exposures to massive amounts of ammonia gas, but the extent of exposure was not quantified (Slot 1938). No information was located regarding cardiovascular effects of ammonia or ammonium in animals following dermal or ocular exposure.

Gastrointestinal Effects. Persistent vomiting was noted by Slot (1938) in human accidental massive exposure cases, but the extent of exposure was not quantified. Oral and pharyngeal burns and edema

Table 3-3 Levels of Significant Exposure to Ammonia And Ammonium Compounds - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE						
Death						
Rat	1 d 30 min/d				71.9 mg/L (LC50)	Prokop'eva et al. 1973
Rat	1 d 60 min/d				48.4 mg/L (LC50)	Prokop'eva et al. 1973
Systemic						
Human	5 min	Ocular	50 ppm	72 ppm (eye irritation)		Industrial Bio-Test Laboratories, Inc. 1973
Human	10 min	Ocular	30 ppm	50 ppm (moderate ocular irritation)		MacEwen et al. 1970
Pig (Duroc)	5 wk min/d	Ocular	10 ppm	50 ppm (ocular irritation)		Stombaugh et al. 1969
INTERMEDIATE EXPOSURE						
Systemic						
Human	6 wk 5 d/wk 6 hr/d	Ocular	25 ppm	50 ppm (transitory eye irritation)		Ferguson et al. 1977

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

were reported by Levy et al. (1964) in four human males accidentally exposed to an unknown quantity of anhydrous ammonia. Inhalation exposure may have contributed to these effects also.

Renal Effects. Renal congestion and hemorrhagic nephritis were reported by Slot (1938) in six cases of accidental human exposures to highly concentrated aerosols of ammonium derived from anhydrous ammonia. The exposure level cannot be determined from the available data.

Dermal Effects. Skin and eyes are extremely sensitive to airborne ammonia or ammonium in water. The topical damage caused by ammonia is probably due mainly to its alkaline properties. Its high water solubility allows it to dissolve in moisture on these surfaces, react with fatty substances in the corneal layer, be absorbed into deeper layers, and inflict extensive damage (Jarudi and Golden 1973). Reports of skin damage in humans are numerous, but good quantitative data are lacking. The severity of the damage is proportional to concentration and duration of exposure; flushing with water immediately after contact alleviates or prevents effects. Burns, blisters, and lesions of the skin have been reported (Close et al. 1980; Flury et al. 1983; Shimkin et al. 1954; Slot 1938; Taplin et al. 1976; Walton 1973). Exposure levels associated with dermal effects are presented in Table 3-3.

Several case reports described exposure of individuals to ammonia liquid and/or gas that resulted in cutaneous burns (Amshel et al. 2000; da Fonseca et al. 1998; George et al. 2000; Kerstein et al. 2001; Latenser and Lucktong 2000; Leduc et al. 1992; Rosenbaum et al. 1998; Weiser and Mackenroth 1989). All exposures were occupationally related. Total body surface area burned ranged from 14 to 45% and most had at least small areas of full-thickness burns that required skin grafting. A summary of 12 case reports of liquid anhydrous ammonia injuries reported a range of percent body surface area burned of 3–22%, with 25% of the patients having full-thickness burn injuries (Millea et al. 1989). One case report included a skin litmus paper test that showed the pH of the skin to be 10 at the time of hospital admission (Amshel et al. 2000). Infection of the burn wounds was not uncommon, with most of the patients responding to antibiotic treatment. One person had facial and neck hyperemia, erythematous petechiae on one ear, and edematous and peeling lips (Latenser and Lucktong 2000). The individual with 45% total body surface area burned had additional severe injuries, including respiratory and ocular, and developed circulatory and hematological problems, which led to his death (George et al. 2000).

Rosenbaum et al. (1998) described two cases of young children (2–3 years old) who bit into ammonia pellets/capsules. Both children drooled and had ulcerative lesions on the tongue and/or on the buccal mucosa. One child had superficial ulcerations on the posterior esophageal wall and the other child had

edematous, erythematous upper and lower lips with areas of desquamation, eschar of the hard palate, and edema and erythema of the supraglottic structures and upper trachea. Both children recovered without incident.

A single case report described a self-administered ammonium solution enema that resulted in anal pain, diffuse abdominal colic, and tenesmus (da Fonseca et al. 1998). Sigmoidoscopy showed diffuse erythematous friable mucosa with large ulcerations covered by yellowish exudate. Six days later, the ulcers had receded, but the colon was still erythematous. Three months postexposure, biopsies showed chronic inflammation and fibrosis of the rectum and sigmoid colon, but no stenosis.

Animal data regarding dermal and ocular effects of exposure to ammonia support the findings in humans. A number of cattle were acutely exposed to anhydrous ammonia fumes when a pipeline running through their pasture ruptured and leaked 1,800 barrels of ammonia in a short period of time (Morgan 1997). The ammonia combined with moisture in the air and formed a white cloud, which drifted south across two additional fields containing cattle. The noses of the cattle in the field with the pipeline turned black and peeled and the horns of cattle in an adjacent field turned black and peeled. Hair coats on all livestock within a 2-mile radius of the rupture were singed.

Ocular Effects. Reported ocular effects in humans following ammonia or ammonium exposure increase in severity with dose and duration. Good quantitative data are lacking, but symptoms progress as follows: inflamed eyes, lacrimation, swelling of the eyelids (Beare et al. 1988; Caplin 1941; Close et al. 1980; Ferguson et al. 1977; Jarudi and Golden 1973; Legters et al. 1981; Montague and Macneil 1980; O'Kane 1983; Price et al. 1983; Silverman et al. 1949; Stombaugh 1969; Verberk 1977; Ward et al. 1983), hyperemic conjunctiva (Caplin 1941; Hatton et al. 1979; Levy et al. 1964; Slot 1938; Sobonya 1977), transient blindness, blurred vision, and corneal abrasions (Latenser and Lucktong 2000), and sustained corneal damage (Caplin 1941; Grant 1974: Kass et al. 1972; McGuinness 1969; Stroud 1981; Yang et al. 1987). Ammonia is slightly irritating to human eyes at concentrations of 100 ppm (Ferguson et al. 1977), and immediately irritating to the eyes and throat at 698 ppm (Henderson and Haggard 1927). Exposure to an air concentration of 250 ppm is bearable for most persons for 30–60 minutes (Withers et al. 1986). Exposure levels associated with ocular effects are presented in Table 3-3.

Animal data regarding ocular effects of exposure to ammonium support the findings in humans. Corneal opacity has been observed in rabbits following brief exposures (2 seconds) to a solution of 28.5% ammonium hydroxide (Grant 1974). Volume administered was not reported. Cattle in an adjacent field

to a pipeline that ruptured and released 1,800 barrels of ammonia had runny eyes; two cows in the same field with the ruptured pipeline were euthanized because of blindness and respiratory distress (Morgan 1997).

3.2.3.3 Immunological and Lymphoreticular Effects

Secondary infections often complicate the clinical outcome of burns and respiratory lesions related to exposures to highly concentrated aerosols derived from anhydrous ammonia in which dermal and ocular exposure accompanies inhalation exposure (Sobonya 1977; Taplin et al. 1976). However, there is no evidence that the decreased immunological resistance represents a primary impairment of the immune system in humans. No information was located regarding the immunological effects of ammonia or ammonium in animals following dermal or ocular exposure.

No information was located regarding the following effects of ammonia or ammonium compounds in humans or animals following dermal or ocular exposure:

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

Carcinogenic potential of ammonia has not been established in humans or animals by the dermal route of exposure. One case report was found of a person who developed epidermal carcinoma of the nasal septum 6 months after being badly burned by accidental contact with a refrigeration ammonia-oil mixture (Shimkin et al. 1954). It is unclear whether ammonia played a role in this tumor development. No other reports were located, although many cases of contact with ammonia from spills have been followed for more than 6 months after exposure.

3.2.4 Other Routes of Exposure

There are limited *in vitro* data suggesting that ammonium ion may affect fetal development (Lane and Gardner 1994). Mouse embryos (conceived *in vivo*) were cultured in modified mouse tubal fluid medium (mMTF) or mMTF supplemented with 300 µmol/L ammonium ion for 48, 69, or 93 hours before being transferred to pseudopregnant mouse dams (Lane and Gardner 1994). Examination on gestational day 15 showed an apparent relationship between the duration of exposure and the incidence of exencephaly. Embryos that were cultured with various concentrations of ammonium ion before being transferred to recipient dams showed increased incidence of exencephaly with increased ammonium concentration (38–300 µmol/L) and decreased percentage of implantation sites with increased ammonium concentration. It is unclear how embryos might be exposed to ammonia or ammonium *in vivo* or if *in vivo* exposure would affect fetal development and implantation in a way similar to that described in the Lane and Gardner (1994) study.

3.3 GENOTOXICITY

A single study examined the genotoxic effect of ammonia in humans (Yadav and Kaushik 1997). Analysis of blood samples from 22 workers exposed to ammonia in a fertilizer factory and 42 control workers not exposed to ammonia showed increased frequency of chromosomal aberrations (CAs) and sister chromatid exchanges (SCEs), increased mitotic index (MI), and increased frequency of CAs and SCEs with increasing length of exposure.

Swiss albino mice administered a single dose of 12, 25, or 50 mg/kg ammonium intraperitoneally had an increased frequency of micronuclei compared to controls (Yadav and Kaushik 1997).

All remaining tests of ammonia's mutagenicity consist of studies in *E. coli*, chick fibroblast cells, and *Drosophila melanogaster* (Table 3-4). Demerec et al. (1951) noted positive effects in a reverse mutation test in *E. coli*, but only in treatments using toxic levels of NH_4^+ (98% lethality). Lobasov and Smirnov (1934) found slight mutagenic activity in *Drosophila* following exposure to ammonia gas, but once again, survival after treatment was <2%. Auerbach and Robson (1947) tested Lobasov and Smirnov's results and noted 0.5% sex-linked lethals. The authors concluded that although their data did not support the earlier study's findings, it is possible that ammonia has a very slight mutagenic action. In their data presentation, however, they report their findings as negative, qualifying it as doubtful and probably negative.

Table 3-4. Genotoxicity of Ammonia *In Vitro* and *In Vivo*

Species (test system)	End point	Form	Activation system	Results		Reference
				With activation	Without activation	
In vitro:						
Escherichia coli	Reverse mutation	NH_3		NT	+ (at toxic levels)	Demerec et al. 1951
Chick fibroblasts	Chromosomal aberrations	NH_4Cl^+ NH_4OH buffer		NT	+	Rosenfeld 1932
Mouse fibroblasts	Reduced cell division	$NH_3^+NH_4Cl$		NT	+	Visek et al. 1972
Mouse fibroblasts (3T3)	Reduced cell division			NT	+	Capuco 1977
Mouse fibroblasts	DNA repair inhibition	NH_4Cl		NT	+	Capuco 1977
In vivo:						
Drosophila melanogaster	Mutagenic lethality	NH_3		+	NT	Lobasov and Smirnov 1934
D. melanogaster	Sex-linked recessive lethal mutations	NH_3		– (doubtful, probably negative)	NT	Auerbach and Robson 1947
D. melanogaster	Dominant lethality	NH_3		–	NT	Auerbach and Robson 1947
Mouse ileal and colonic mucosa cells	Decreased rate of DNA synthesis	NH_4Cl		NT	+	Zimber and Visek 1972a

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid; NH_3 = ammonia; NH_4Cl = ammonia chloride; NH_4OH = ammonium hydroxide; NT = not tested

In vitro tests of chick fibroblast cells showed that buffered ammonia-ammonium chloride solutions can induce clumping of chromosomes, inhibit spindle formation, and result in polyploidy (Rosenfeld 1932). Visek et al. (1972) noted reduced cell division in mouse fibroblasts cultured in media to which ammonia and ammonium chloride were added. The effect was noted in cultures irrespective of pH. Decreased rate of DNA synthesis was noted in mouse mucosal cells in the ileum and colon when serum NH_4^+ levels were significantly elevated over normal levels; these elevated levels were induced by intraperitoneal injection of urease or infusion of ammonium chloride (Zimber and Visek 1972a).

Iwaoka et al. (1981), responding to controversy regarding mutagenicity in fried hamburgers, found that extraction of organic ingredients from fried hamburger and refrigerated biscuit products with ammonium hydroxide or ammonium sulfate increased mutagenic activities in *Salmonella typhimurium* T98 and TA1538 Ames' microsomal systems, while negative results were obtained from extraction with sodium sulfate. The mode of action is unclear; ammonium salts may in some way affect the mutagenic activities of some agents, or they may simply be more efficient extractors of mutagenic components from these foods.

Taken together, the data indicate that ammonia and ammonium ion may have clastogenic and mutagenic properties.

3.4 TOXICOKINETICS

Studies suggest that ammonia can be absorbed by the inhalation and oral routes of exposure, but there is less certainty regarding absorption through the skin. Absorption through the eye has been documented. Most of the inhaled ammonia is retained in the upper respiratory tract and is subsequently eliminated in expired air. Almost all of the ammonia produced endogenously in the intestinal tract is absorbed. Exogenous ammonia is also readily absorbed in the intestinal tract. Ammonia that reaches the circulation is widely distributed to all body compartments although substantial first pass metabolism occurs in the liver where it is transformed into urea and glutamine. Ammonia or ammonium ion reaching the tissues is taken up by glutamic acid, which participates in transamination and other reactions. The principal means of excretion of ammonia that reaches the circulation in mammals is as urinary urea; minimal amounts are excreted in the feces and in expired air.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Experiments with volunteers show that ammonia, regardless of its tested concentration in air (range, 57–500 ppm), is almost completely retained in the nasal mucosa (83–92%) during short-term exposure, i.e., up to 120 seconds (Landahl and Herrmann 1950). However, longer-term exposure (10–27 minutes) to a concentration of 500 ppm resulted in lower retention (4–30%), with 350–400 ppm eliminated in expired air by the end of the exposure period (Silverman et al. 1949), suggesting an adaptive capability or saturation of the absorptive process. Nasal and pharyngeal irritation, but not tracheal irritation, suggests that ammonia is retained in the upper respiratory tract. Unchanged levels of blood-urea-nitrogen (BUN), non-protein nitrogen, urinary-urea, and urinary-ammonia are evidence of low absorption into the blood. Exposure to common occupational limits of ammonia in air (25 ppm) with 30% retention (and assuming this quantity is absorbed into the blood stream) would yield an increase in blood ammonium concentration of 0.09 mg/L (calculated by WHO 1986). This calculated rise is only 10% above fasting levels, as reported by Conn (1972).

Animal data provide supporting evidence for high-percentage nasal retention, thus protecting the lower respiratory tract from exposure (Dalhamn [1963] and Boyd et al. [1944], rabbit; Egle [1973], dog). Continuous exposure of rats for 24 hours to concentrations up to 32 ppm resulted in significant increase in blood ammonia levels (Schaerdel et al. 1983). Exposures to 310–1,157 ppm led to significantly increased blood concentrations of ammonia within 8 hours of exposure initiation, but blood ammonia returned to pre-exposure values within 12 hours of continuous exposure and remained so over the remaining of the 24-hour exposure period. This suggests an adaptive response mechanism may be activated with longer-term exposure (Schaerdel et al. 1983).

3.4.1.2 Oral Exposure

Case reports of human ingestion of household ammonia (ammonium hydroxide) provide evidence of its absorption by this route, but few provide quantitative data. For example, in a fatal case of a man who drank an unknown amount of a 2.4% solution of ammonium hydroxide, analysis of the contents of the stomach and blood showed ammonium ion concentrations of 153 and 33 ppm, respectively (Klendshoj and Rejent 1966). In a study of volunteers, ingestion of a single ammonium chloride tablet (approximately 15 mg NH_4^+/kg/day) led to a small transient increase (33% above fasting levels) in arterial

blood concentrations of ammonium ion in 11 out of 20 subjects (Conn 1972); no change was noted in the remaining nine subjects in this group. Among 50 cirrhotic patients, increases of about 150% were noted in arterial blood concentrations of ammonium ion and return to normal levels was slow (Conn 1972). These data indicate that ingested ammonia is readily absorbed from the digestive tract and that the liver plays a large role in removing it from the blood (Conn 1972). Analysis of urine samples from subjects on high and low protein diets and given ^{15}N-ammonium chloride, showed that 30–65% of labeled nitrogen from ^{15}N-ammonium chloride is absorbed and metabolized (Richards et al. 1975). Oral administration of $^{15}NH_4Cl$ to a group of six subjects for six days resulted in absorption of at least 38.7% of the administered radioactivity as determined by the amount of ^{15}N that appeared in urinary urea within 24 hours of the last $^{15}NH_4Cl$ ingestion (Metges et al. 1999).

Ammonium ion is endogenously produced in the human digestive tract, much of it arising from the bacterial degradation of nitrogenous compounds from ingested food. About 4,200 mg/day are produced, greater than 70% of which is synthesized or liberated within the colon and its fecal contents. The total amount absorbed is about 4,150 mg/day, or 99% of the amount produced (Summerskill and Wolpert 1970); absorption after oral loading of NH_4^+ is similarly complete (Fürst et al. 1969). Evidence from Castell and Moore (1971) and Mossberg and Ross (1967) suggests that absorption of NH_4^+ increases as the pH of the contents of the lumen increases, and that the ammonium ion is actively transported at the lower pH levels (pH 5 was lowest detected absorption). Ammonium ion absorbed from the gastrointestinal tract travels via the hepatic portal vein directly to the liver, where in healthy individuals, most of it is converted to urea and glutamine. Human and animal data show that little of it reaches the systemic circulation as ammonia or ammonium compounds, but that it is a normal constituent of plasma at low levels (Brown et al. 1957; Pitts 1971; Salvatore et al. 1963; Summerskill and Wolpert 1970). Analysis of plasma drawn from 10 healthy young male subjects yielded endogenously derived NH_4^+ concentrations ranging from 30 to 55 μg NH_3/100 mL, with a mean of 39 μg/100 mL (Brown et al. 1957).

3.4.1.3 Dermal Exposure

Quantitative data on absorption from exposure by the dermal route were not located in the available literature. Human case reports of dermal exposure describe local damage (burns, irritations). One report of case histories of five persons exposed to an exploding, bursting anhydrous ammonia gas pipe indicated there was systemic toxicity (vomiting, renal congestion, delirium), but exposure was by inhalation as well as dermal route, and it is impossible to delineate a systemic dermal exposure contribution (Slot 1938).

WHO (1986) concluded that systemic effects from skin and eye exposure are not quantitatively important. Ammonia is readily absorbed into the eye; it was found to diffuse within seconds into cornea, lens, drainage system, and retina (Beare et al. 1988; Jarudi and Golden 1973). However, amounts absorbed were not quantified, and absorption into systemic circulation was not investigated.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No quantitative reports of distribution of ammonia from inhalation exposure were found in the available literature. Absorption data from human inhalation exposure suggest that only small amounts of ammonia are absorbed into the systemic circulation (Silverman et al. 1949; WHO 1986). Initial retention of inhaled ammonia in the mucus of the upper respiratory tract may be 80% or more, but after equilibrium is established (within 30 minutes) 70–80% of inspired ammonia is expired in exhaled air (Silverman et al. 1949). The lack of change in blood nitrogen compounds and urinary-ammonia compounds lends further support to a limited absorption into the systemic circulation (Silverman et al. 1949). Toxic effects reported from inhalation exposure suggest local damage, or changes resulting from necrotic tissue degradation, rather than the presence of elevated levels of NH_4^+, *per se*, in tissues other than the respiratory/pharyngeal tissues. Information on the distribution of endogenously-produced ammonia suggests that any NH_4^+ absorbed through inhalation would be distributed to all body compartments via the blood, where it would be used in protein synthesis or as a buffer, and that excess levels would be reduced to normal by urinary excretion, or converted by the liver to glutamine and urea. If present in quantities that overtax these organs, NH_4^+ is distributed to other tissues and is known to be detoxified in the brain (Takagaki et al. 1961; Warren and Schenker 1964).

3.4.2.2 Oral Exposure

Human oral exposure data for NH_4^+ clearly indicate that it readily enters the portal circulation and is delivered to the liver (Conn 1972; Fürst et al. 1969), as has been shown to be the case for endogenously produced NH_4^+ (Pitts 1971; Summerskill and Wolpert 1970). In nitrogen-deficient persons, NH_4^+ (as ammonium acetate) administered orally was absorbed and carried directly to the liver where most of it was converted to urea and excreted in the urine; little change in the negative nitrogen balance was observed (Fürst et al. 1969). Output of urea from the liver corresponded to the amount of NH_4^+ ingested (Fürst et al. 1969).

Un-ionized ammonia is freely diffusible, whereas the ammonium ion is less so and is relatively confined to the extracellular compartment (Stabenau et al. 1958). However, ammonium ion is in dynamic equilibrium with dissolved ammonia. Therefore, ammonium compounds that enter the circulatory system or other body fluids can thus freely penetrate tissue cells as ammonia. In hypophysectomized rats that were administered ^{15}N-ammonium citrate orally by gavage, labeled protein was found in liver, kidney, spleen, heart, and skeletal muscle 6–72 hours after ^{15}N-ammonium citrate administration (Vitti et al. 1964). The percentages of ingested label absorbed and then excreted as urea in the urine were not provided (Vitti et al. 1964).

3.4.2.3 Dermal Exposure

No quantitative data on distribution of ammonia from dermal exposure were located in the available literature. Toxic effects from dermal exposure suggest that little or no ammonia gains entry into the systemic circulation by this route.

3.4.2.4 Other Routes of Exposure

Intravenous administration of NH_4^+ (as ammonium salts) to people with a nitrogen deficiency (in negative nitrogen balance) resulted in an increase in the peripheral blood NH_4^+ level and a shift in the nitrogen balance from negative to positive; no increase in urinary urea was seen (Fürst et al. 1969). The nitrogen from NH_4^+, which gains entry into the general circulation, is distributed to cells throughout the body and incorporated into tissues (Fürst et al. 1969; Vitti et al. 1964). After intraperitoneal injection of ammonium chloride in mice, ammonia distributes to brain tissues within 20 seconds (Warren and Schenker 1964), and in rats, brain concentrations increase dramatically within 5 minutes (Salvatore et al. 1963). Tissues other than blood and brain were not analyzed by these researchers. Comparative patterns of distribution of ^{15}N-labeled ammonium citrate indicate that the amount of NH_4^+ taken up by tissues other than the liver is greatest by subcutaneous injection, less by intraperitoneal injection, and least following intragastric administration. Intravenous administration of ^{15}N-labeled ammonium salts leads to rapid distribution of ^{15}N-labeled metabolites throughout the body, with the highest levels of labeled urea appearing in the kidney and liver, and lesser amounts in heart, spleen, brain, testes, and carcass. Highest levels of labeled glutamine were found in heart and liver, with lesser amounts in brain, spleen, carcass, kidney, and testes (Duda and Handler 1958).

3.4.3 Metabolism

Quantitative data on human metabolism of exogenously introduced ammonia were not located in the available literature. Ammonia and ammonium ion are metabolized to urea and glutamine mainly in the liver by the process diagrammed in Figures 3-3 and 3-4 and described by Fürst et al. (1969) and Pitts (1971). However, it can be rapidly converted to glutamine in the brain and other tissues as well (Takagaki et al. 1961; Warren and Schenker 1964). The nitrogen is released from glutamine within tissue cells and used for protein synthesis as needed (Duda and Handler 1958; Fürst et al. 1969; Richards et al. 1975; Vitti et al. 1964). Ingestion of ammonium salts leads to almost complete conversion of ammonium ion into urea in the liver, whereas exposure by other routes may lead to its metabolism in body tissues to glutamine or tissue protein (Fürst et al. 1969; Vitti et al. 1964).

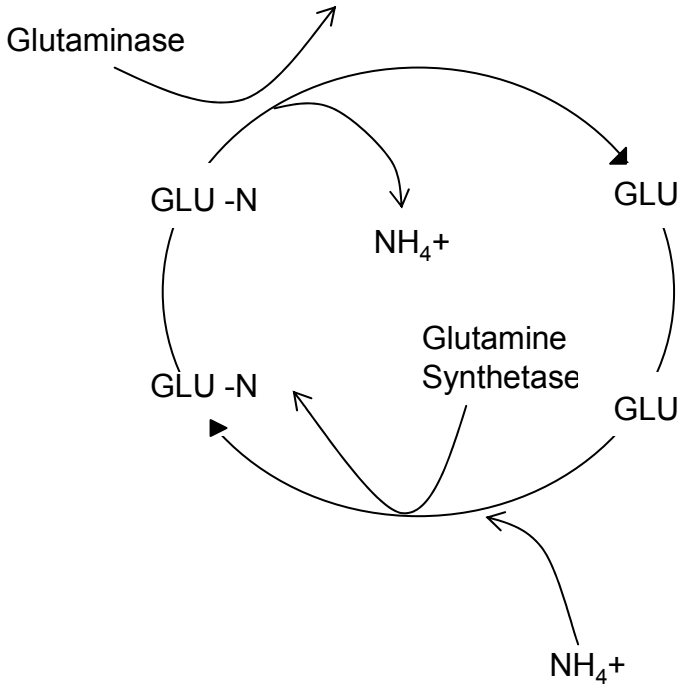
Duda and Handler (1958) administered 0.03 mg/kg body weight of ^{15}N-ammonium acetate intravenously to rats and noted that 90% was converted to glutamine and urea within 30 minutes, with glutamine being the major early product. Labeled nitrogen was also found in amino acids, purines, pyrimidines, and other nitrogenous compounds. Morimoto et al. (1988) found that the amount of ^{15}N from an intravenous injection of ammonium chloride to rats that was taken up into glutamine-amide-N and urea-N reached a peak at 5 minutes and decreased gradually from 15 to 60 minutes after the injection. This finding suggests that urea synthesis and glutamine synthesis occurred simultaneously within minutes after the injection, and glutamine-amide-N is gradually transferred to the urea cycle from 15 to 60 minutes following dosing. Low amounts (0.008% of a 17 mg oral dose) of ^{15}N-ammonium chloride administered repeatedly to rats were converted to ^{15}N-nitrate in the urine (Saul and Archer 1984).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Studies using low levels of ammonia show that inhaled ammonia is temporarily dissolved in the mucus of the upper respiratory tract, and then a high percentage of it is released back into the expired air. Following exposure to 500 ppm ammonia for 10–27 minutes, healthy male subjects eliminated 70–80% of the inspired ammonia by this route (Silverman et al. 1949). Analysis of endogenous ammonia levels in the expired air of rats showed concentrations ranging from 10–353 ppb (mean=78 ppb) in nose-breathing animals (Barrow and Steinhagen 1980).

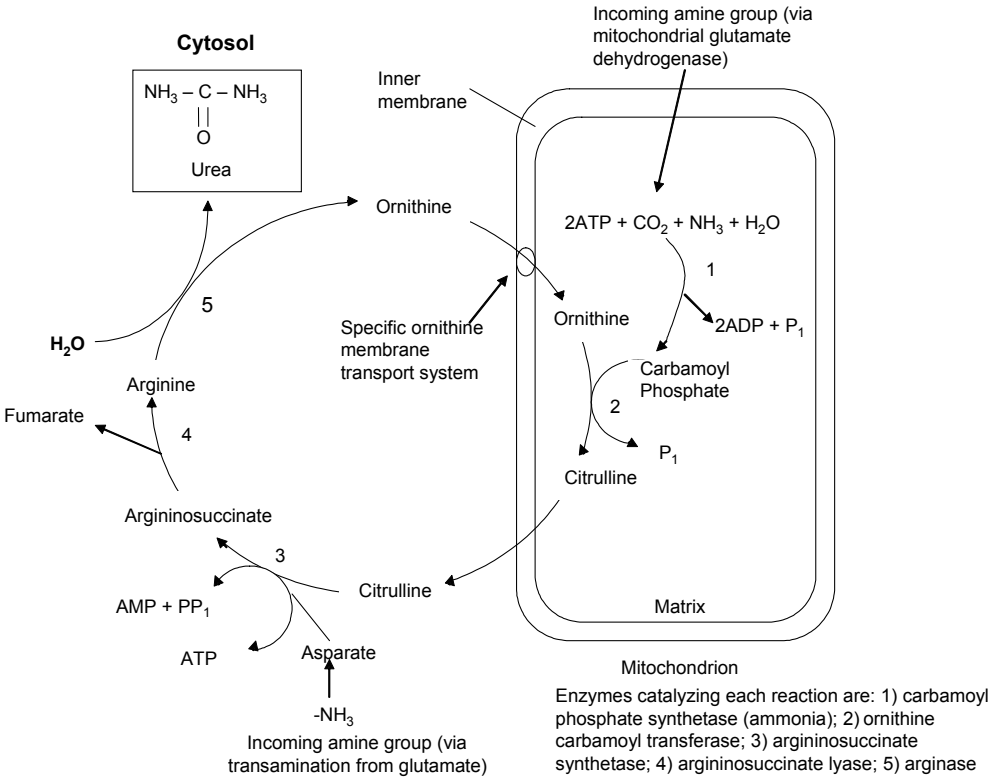
Figure 3-3. Glutamine Cycle



GLU = Glutaminate; GLU-N = Glutamine

Source: Brunner and Thaler 1981

Figure 3-4. The Urea Cycle Showing the Compartmentalization of its Steps Within Liver Cells



Source: Lehninger 1975

The quantitative difference between inspired and expired ammonia suggests that small amounts are absorbed across the nasopharyngeal membranes into the systemic circulation. Absorbed ammonia is excreted by the kidneys as urea and urinary ammonium compounds (Gay et al. 1969; Pitts 1971; Richards et al. 1975; Summerskill and Wolpert 1970), as urea in feces (Richards et al. 1975), and as components of sweat (Guyton 1981; Wands 1981), but quantitative data are lacking. Toxic levels do not develop as a result of chronic inhalation exposure because the body has multiple effective mechanisms for detoxifying and excreting it.

3.4.4.2 Oral Exposure

Excretion data for humans orally exposed to ammonia have been quantified with respect to excretion of isotope from ^{15}N-labeled ammonium salts, thus providing an indication of the turnover rate of the compound within the body and excretion route of its metabolites. Approximately 72% of a dose of ^{15}N was excreted in the urine of three subjects within 3 days of ingestion of ammonium salts in drinking water; 25% (24% urinary urea and 1% urinary NH_4^+) was eliminated within the first 6 hours after exposure. Ammonium salt administered by gavage to humans led to a corresponding increase in blood urea concentration transported out of the liver, leading the authors (Fürst et al. 1969) to conclude that orally ingested ammonium salt is quickly and almost completely converted in the liver and eliminated from the body as urinary urea. Analysis of urine samples from subjects on high and low protein diets showed higher cumulative excretion of ^{15}N (percent of dose) in the urine of the high protein group (approximately 70%) than that of the low protein group (35%). Small amounts of labeled nitrogen were also excreted as urea in feces (Richards et al. 1975).

These data correspond to that for excretion of endogenously produced ammonia (Davies and Yudkin 1952; Muntwyler et al. 1956; Summerskill and Wolpert 1970; Van Slyke et al. 1943). Ammonia is also known to be excreted via sweat (Guyton 1981; Wands 1981) and expired air (Barrow and Steinhagen 1980; Larson et al. 1980; Robin et al. 1959; Utell et al. 1989); quantitative data are unavailable for excretion via sweat.

3.4.4.3 Dermal Exposure

Data regarding excretion of ammonia absorbed following dermal exposure were not located in the available literature.

3.4.4.4 Other Routes of Exposure

Data are available on exposure of humans and dogs to ammonium salts by intravenous injection. Excretion of isotope after ^{15}N-ammonium lactate injection in three human subjects yielded 5–7% of isotope excreted as urinary NH_4^+ in the first 6 hours postexposure, and another 2% within 3 days. Approximately 6% of the isotope was excreted as urea in urine in the first 6 hours. An average of approximately 60% of the dose of label was excreted in urine within 3 days. These data are considerably different from that resulting from oral loading (as described in Section 3.4.4.2). Intravenous loading led to decreased labeling of urinary urea and grossly increased labeling of urinary ammonia; the differences are attributed by the authors to a "first pass" effect from oral loading (Gay et al. 1969). The hepatic transformation of ammonium ion to urea is so efficient that relatively little unconverted ammonium salt is released to the general circulation.

Intravenous exposure of seven dogs to 107 mg/kg ammonium acetate led to amounts ranging from 0.044 to 0.073 mg ammonia excreted in expired air. No measurable amount of ammonia was present in expired air during the pre-exposure control period (Robin et al. 1959).

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 et al. 1987; Andersen and Krishnan 1994). 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.

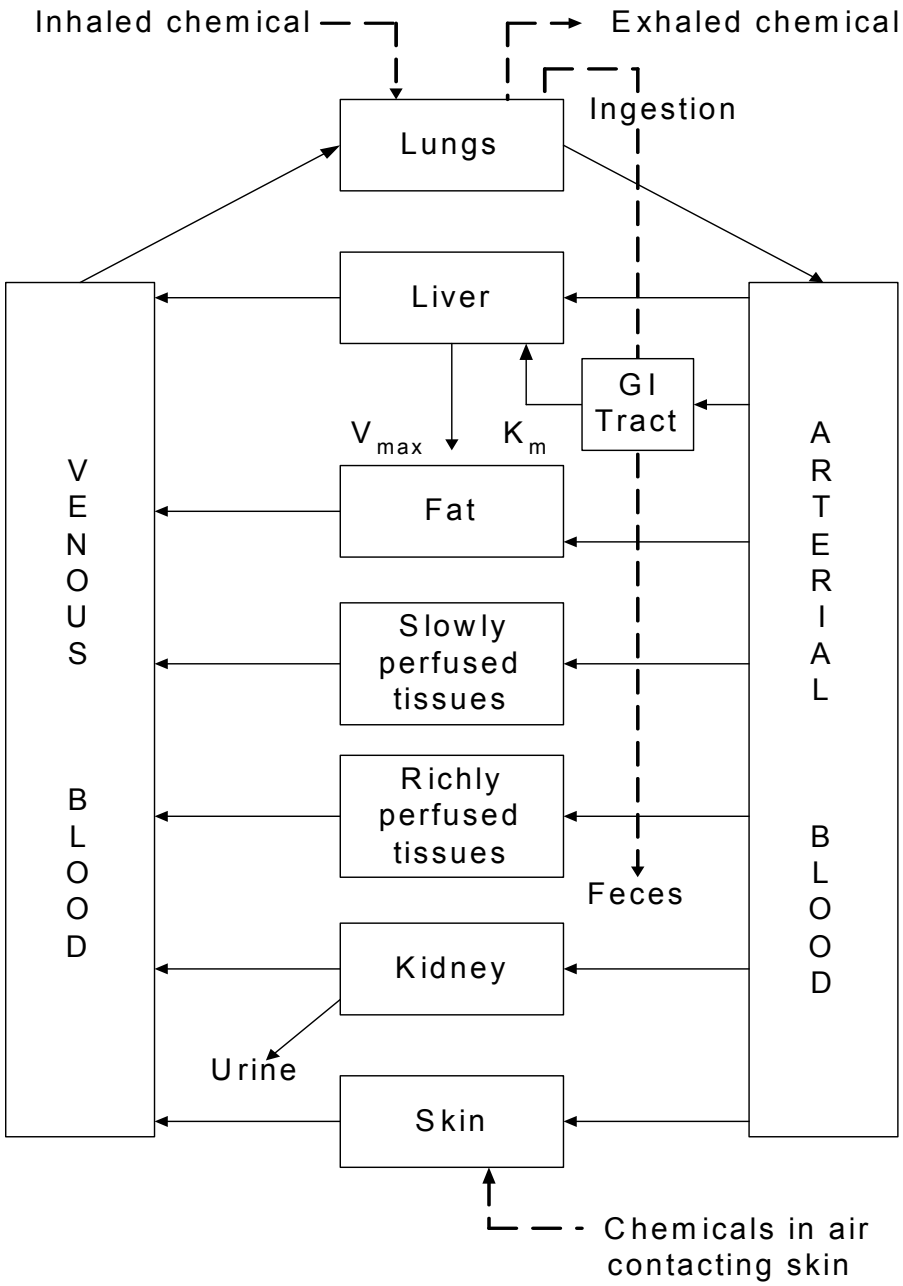
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically 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) is 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 data regarding PBPK models for ammonia were located.

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

Data regarding the pharmacokinetic mechanisms of ammonia were not located in the available literature.

3.5.2 Mechanisms of Toxicity

Ammonia is an irritant and the primary and most immediate effect of ammonia exposure is burns to the skin, eyes, and respiratory tract. The topical damage caused by ammonia is probably due mainly to its alkaline properties. Its high water solubility allows it to dissolve in moisture on the mucous membranes, skin, and eyes, forming ammonium hydroxide, which causes liquefaction necrosis of the tissues (Jarudi and Golden 1973). Specifically, ammonium hydroxide causes saponification of cell membrane lipids, resulting in cell disruption and death. Additionally, it extracts water from the cells and initiates an inflammatory response, which further damages the surrounding tissues (Amshel et al. 2000). Contact with liquid ammonia results in cryogenic injury in addition to the alkali burns (Amshel et al. 2000; Wibbenmeyer et al. 1999).

Excess circulating levels of ammonia (hyperammonemia) can cause serious neurological effects. Hyperammonemias can be inherited (i.e., inborn errors of urea cycle enzymes) or acquired (i.e., liver toxicity caused by ingested toxins, viral infections, autoimmune disease) (Felipo and Butterworth 2002). An extensively studied neuropsychiatric disorder known as hepatic encephalopathy develops when liver function is impaired and the organ cannot metabolize ammonia. This results in an increased concentration of ammonia in the blood and brain. The mechanism of ammonia-induced encephalopathies has not been definitively elucidated, but is thought to involve the alteration of glutamate metabolism in the brain and resultant increased activation of NMDA receptors (Felipo et al. 1993; Marcaida et al. 1992), which causes decreased protein kinase C-mediated phosphorylation of Na^+/K^+ ATPase, increased activity of Na^+/K^+ ATPase, and depletion of ATP (Kosenko et al. 1994). Antagonists of NMDA receptors, agonists of metabotropic glutamate receptors, agonists of muscarinic receptors, and inhibitors of protein kinase C, calcineurin, or nitric oxide synthase prevent glutamate toxicity, indicating that all of these play a role in acute ammonia neurotoxicity (Felipo et al. 1998). Additional evidence of altered energy levels include changes in some TCA cycle-associated components including acetoacetate, and NAD^+/NADH ratio, 2-oxoglutarate, and 3-hydroxybutarate (Kosenko et al. 1993). A disruption in neurotransmission

has also been suggested by alteration of brain tubulin, which is an essential component of the axonal transport system (Miñana et al. 1989a, 1989b).

During certain disease states that result in renal tubular injury, NH_4^+ production by renal proximal tubules may increase in order to maintain net acid excretion. However, this may also contribute to further renal damage by modifying the third component of complement and initiating the alternative complement pathway (Clark et al. 1990). Ammonia can chemically interact with an internal thiolester bond of complement 3 (C3), resulting in an amide linkage and a subsequent conformational change of the C3. The altered C3 then activates the alternative complement pathway, which causes the release of chemoattractants and the assembly of the membrane attack complex of complement (Clark et al. 1990). Amidated C3 can also bind directly to phagocyte complement receptors, which causes the release of toxic oxygen species (Clark et al. 1990). It has also been suggested that NH_4^+ depresses protein degradation in renal cells and inhibits renal cell replication, which supports the findings of renal hypertrophy in renal injury and indicates that NH_4^+ may inhibit recovery from injury (Rabkin et al. 1993).

Ammonium ion may also contribute to adverse effects of *Helicobacter pylori* on the stomach. *H. pylori* produces urease, which breaks down urea that is normally present in the stomach into ammonia (Mégraud et al. 1992; Tsujii et al. 1992a). An *in vitro* study that examined the effects of ammonia produced by *H. pylori* on HEp2 cells showed increased cell vacuolation and viability of the cells compared to a urease-negative variant of the same cells (Mégraud et al. 1992). An *in vivo* study suggested that NH_4^+ also causes macroscopic gastric lesions and increases the release of endothelin-1 (ET-1) and thyrotropin releasing hormone (TRH) from the gastric mucosa, probably via an endothelin A (ET_A) receptor, which exerts ulcerogenic action on the gastric mucosa (Mori et al. 1998). Ammonia may also trigger the release of cysteine proteases in the stomach that contribute to the development of gastric hemorrhagic mucosal lesions (Nagy et al. 1996). Neutrophils that migrate to the gastric mucosa in response to the presence of *H. pylori* may release hypochlorous acid, which can interact with NH_4^+ to produce the powerful cytotoxic oxidizing agent monochloramine (Murakami et al. 1995).

3.5.3 Animal-to-Human Extrapolations

The primary effects of ammonia in humans are due to its corrosive and irritative properties. Exposure to ammonia gas causes damage to the respiratory tract, eyes, and skin when the ammonia combines with water to become ammonium hydroxide, which results in liquefaction necrosis of the tissues, cell structural breakdown, and inflammatory damage (Amshel et al. 2000; Wibbenmeyer et al. 1999). Animal studies

have indicated similar types of injuries of the respiratory tract (Coon et al. 1970; Kapeghian et al. 1982; Mayan and Merilan 1972; Richard et al. 1978a, 1978b; Schaerdel et al. 1983; Stombaugh et al. 1969), eyes, and skin (Morgan 1997).

Oral exposure of humans to high concentrations of ammonia and ammonium hydroxide has been shown to result in buccal, esophageal, and upper tracheal burns and edema (Christesen 1995; Klein et al. 1985; Rosenbaum et al. 1998), but no reports of the effects of ammonia on the stomach or upper gastrointestinal tract in humans have been found. One report of an ammonia enema in a human showed diffuse erythematous, friable mucosa, and large exudative ulcerations in the sigmoid colon and rectum (da Fonseca et al. 1998). Gavage studies in rats have shown similar lesions of the gastric mucosa with notable histopathological effects (Mori et al. 1998; Takeuchi et al. 1995; Tsujii et al. 1993). Rats, therefore, appear to be an adequate model for the primary effects of ammonia in humans. However, humans are unlikely to be orally exposed to amounts of ammonia that would result in the gastric lesions seen in rats. Elevated levels of endogenously produced ammonia resulting from disease states apparently may cause or contribute to gastric pathology (Mégraud et al. 1992; Mori et al. 1998; Tsujii et al. 1992a).

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 Environmental Protection Agency (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), which in 1998 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 toxicity mediated through the endocrine axis in humans after exposure to ammonia. Two studies examined the effects of induced hyperammonemia (with infusion of ammonium chloride) in steers on circulating and portal-drained visceral flux of metabolites and on pancreatic hormones (Fernandez et al. 1988, 1990). Plasma glucose increased 12% during infusion of ammonium chloride (Fernandez et al. 1988, 1990). Plasma insulin decreased up to 46% during ammonium chloride infusion, and then increased up to 122% after infusion was halted (Fernandez et al. 1988); portal-drained visceral release of insulin did not increase during ammonium chloride infusion even with the rise in plasma glucose levels, but increased 109% after cessation of infusion (Fernandez et al. 1990). These data indicate that hyperammonemia in steers may cause reduced hepatic glucose output and glucose-mediated pancreatic insulin release.

No *in vitro* studies were located regarding toxicity mediated through the endocrine axis by ammonia.

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).

Human and animal data indicate that the primary effects of ammonia are irritation and burns and that the primary targets of ammonia are the respiratory tract, eyes, and skin (Burns et al. 1985; Close et al. 1980; Couturier et al. 1971; de la Hoz et al. 1996; Flury et al. 1983; George et al. 2000; Hatton et al. 1979; Heifer 1971; Holness et al. 1989; Kerstein et al. 2001; Latenser and Lucktong 2000; Leduc et al. 1992; Millea et al. 1989; Morgan 1997; Price et al. 1983; Shimkin et al. 1954; Slot 1938; Sobonya 1977; Taplin et al. 1976; Verberk 1977; Weiser and Mackenroth 1989). There are limited data on the toxicity of ammonia in children and no information on effects in adults who were exposed as children. Children (8–9 years old) who attended two schools in the vicinity of a fertilizer plant had higher incidences of acute respiratory diseases than children who attended a school 20 kilometers away (Gomzi 1999; Gomzi and Šarić 1997). Incidence was related to levels of measured pollutants (ammonia, hydrogen fluoride, nitrogen dioxide, total suspended particulate matter, and smoke) in the inside and outside air (Gomzi and Šarić 1997). Forced expiratory volumes were not statistically different between the three schools (Gomzi and Šarić 1997). These results indicate that exposure to low levels of ammonia (0.04–0.23 ppm) or other airborne pollutants may not cause functional respiratory deficits, but may lower the resistance to respiratory pathogens in children. There is no indication that children are more susceptible to the effects of ammonia than adults. However, children have greater surface area to body weight and lung surface area to body weight ratios, and increased minute volume to weight ratio, so they may receive a higher dose than adults in the same situation. Children may also tend to be exposed longer than adults because they may not be as quick as adults to evacuate a contaminated area.

There are no studies that indicate that metabolism of ammonia differs between children and adults. Ammonia is eliminated from the body mainly by processing through the urea cycle in the liver, and urea is then eliminated in the urine and feces. The urea cycle is fully functional in infants at birth; therefore, it is not expected that infants or children are at greater risk of hyperammonemia. Neurotoxicity resulting from hyperammonemia involves alteration of levels of some components of the citric acid cycle, which leads to depletion of ATP, and starvation of brain cells, and depletion of glutamate, a precursor to the neurotransmitter γ-aminobutyrate (GABA). It is not expected that children are more susceptible than adults to ATP depletion via this mechanism.

Infants under 6 months of age may be more sensitive than adults to the effects of high levels of nitrates (from nitrification of ammonia in fertilizers) that may be present in groundwater and well water (Payne

1981). Infants who consume formula and food made with contaminated water from these sources may develop methemoglobinemia, which results in decreased delivery of oxygen to the tissues.

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

There are no known specific biomarkers of exposure for ammonia. Identification of biomarkers of exposure to ammonia is confounded because large amounts of ammonia are produced endogenously. Pharmacokinetic studies reveal that after inhalation exposure to low levels of ammonia, BUN, nonprotein nitrogen, urinary-urea, and urinary-ammonia levels do not change (Silverman et al. 1949). Exposure to common occupational limits of ammonia in air (25 ppm) yield increased blood-ammonia levels only 10% above fasting levels (WHO 1986). In one human study, oral ingestion of ammonium chloride tablets (approximately 15 mg NH_4^+/kg) yielded only a transient increase in blood-ammonia above fasting levels in 11 out of 20 subjects tested; no increase was observed in the remaining 9 subjects (Conn 1972).

3.8.2 Biomarkers Used to Characterize Effects Caused by Ammonia

Effect biomarkers of ammonia exposure are limited to site-of-contact tissue injuries. Upon inhalation exposure, distribution of ammonia is usually limited to the respiratory tract and involves irritation and, at higher concentrations, pulmonary edema and necrosis (Kapeghian et al. 1982; Richard et al. 1978b; Silverman et al. 1949). Oral exposure to high doses of ammonium chloride has produced pulmonary edema in animals (Koenig and Koenig 1949). Dermal exposure to ammonia causes skin and eye irritation and, at higher concentrations, necrosis (Amshel et al. 2000; da Fonseca et al. 1998; George et al. 2000; Kerstein et al. 2001; Latenser and Lucktong 2000; Leduc et al. 1992; Rosenbaum et al. 1998; Weiser and Mackenroth 1989). The severity of injuries by all routes of exposure are dose-related. Unfortunately, these effect biomarkers are not specific for ammonia and can be caused by a variety of caustic substances.

The tissues and organs most sensitive to ammonia exposure are mainly dependent on route of exposure. After inhalation exposure, which can involve a significant dermal exposure, the skin and eyes and the respiratory tract, including the lungs, are most sensitive. Direct dermal exposure produces dose-related effects from irritation to necrosis. Ingestion of ammonium hydroxide has resulted in oral, pharyngeal, and

esophageal lesions (Christesen 1995; Klein et al. 1985). The tissue and organ injuries produced by ammonia, however, are of limited value as biomarkers to characterize the effects caused by ammonia because many other caustic chemicals can produce similar injuries.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Exposure to substances that would increase the pH of exposed tissues could be expected to enhance the alkalotic effects of ammonia, and vice versa. Agents acting to elevate the intestinal-tract pH would increase its local irritant effect, and would promote its absorption as well (Castell and Moore 1971).

Co-administration of ammonia and diethyl pyrocarbonate induced lung tumors in Kid:CFLP mice, while neither agent administered intragastrically and separately was carcinogenic; this effect is believed to be a result of a compound, urethane (a known carcinogen), produced by their interaction (Uzvolgyi and Bojan 1980, 1985). Sprague-Dawley rats given intrarectal doses of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and ammonium acetate had a higher incidence of tumors than did controls that were administered distilled water in place of ammonium acetate (Clinton et al. 1988). The role of acetate was not ruled out. Ammonia acted synergistically with potassium ions on pyruvate kinase, a known Ehrlich ascites tumor enzyme (Olavarria et al. 1986).

Some compounds play a synergistic role with ammonia in producing hepatic coma. Simultaneous injection of an ammonium salt and a fatty acid in Holtman or Sprague-Dawley rats produced coma at lower plasma levels than did injection of either compound separately. Inhalation of methanethiol or injection with sodium octanoate blocked metabolism of an injected dose of ammonium acetate and led to elevated blood ammonia levels (Zieve et al. 1974).

Data regarding exposure to mixtures of atmospheric contaminants indicate that, contrary to what might be expected, increased carbon dioxide concentration (up to 5% in air) does not alter the hyperventilatory rate induced by hyperammonemia in dogs (Herrera and Kazemi 1980). Ammonia in expired air may neutralize inhaled acid aerosols (EPA 1979; Larson et al. 1980; Utell et al. 1989).

Other substances to which people have been exposed have been shown to alter the toxic effects of ammonia. Methionine sulfoximine, administered by intraperitoneal injection, suppressed the tonic convulsions produced by intravenous injection of ammonium chloride in mice (Hindfelt and Plum 1975; Warren and Schenker 1964). Intraperitoneal injection of alpha-methylglutamic acid also exerts a

protective effect against hyperammonemia in rats (Lamar 1970). Nicotinohydroxamic acid and neomycin administered orally reduce blood ammonia levels and increase excretion of urea in treated rats (Harada et al. 1985). Ethanol exerted a protective effect on acute ammonia intoxication in mice (O'Connor et al. 1982), although ethanol was reported to increase ammonia concentrations in body tissues of treated rats (Mohanachari et al. 1984).

Sodium benzoate decreased urea production in ammonia challenged rats (Maswoswe et al. 1986) and hyperammonemic mice (O'Connor et al. 1987). Valproate, a widely used antiepileptic drug, has a hyperammonemic effect in Wistar rats (Ferrier et al. 1988) and may therefore predispose to ammonia intoxication. Ammonia interferes with the metabolism of pent-4-enoic acid in cultured rat hepatocytes and may dramatically potentiate its toxicity (Coude and Grimber 1984).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

Persons who suffer from severe liver or kidney disease may be susceptible to ammonia intoxication, as it is chiefly by the actions of these organs that NH_4^+ is biotransformed and excreted (Córdoba et al. 1998; Gilbert 1988; Jeffers et al. 1988); individuals with hereditary urea cycle disorders are also at risk (Schubiger et al. 1991). In these individuals, the levels produced endogenously are sufficient to produce toxicity. Levels that are likely to be encountered in the environment, with the exception of those resulting from high-level accidental exposures, are insignificant, due to the low absorption rate, in comparison with levels produced within the body (WHO 1986).

Since ammonia is a respiratory tract irritant, persons who are hyperreactive to other respiratory irritants, or who are asthmatic, would be expected to be more susceptible to ammonia inhalation effects. The results of an epidemiological study of a group of workers chronically exposed to airborne ammonia indicate that ammonia inhalation can exacerbate existing symptoms including cough, wheeze, nasal complaints, eye irritation, throat discomfort, and skin irritation (Ballal et al. 1998).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to ammonia. 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 ammonia. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide general information about treatment following exposures alkalies:

Ellenhorn MJ, Barceloux DG. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. New York, NY: Elsevier.

Haddad LM, Shannon MW, Winchester JF, eds. 1998. Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: W.B. Sanders Company.

3.11.1 Reducing Peak Absorption Following Exposure

Absorption of ammonia via dermal exposure is not sufficient to be of concern, but immediate flushing of exposed skin with water or saline will limit dermal damage and reduce dermal absorption of ammonia. It is highly unlikely that enough ammonia could be ingested to be of danger via absorption from the intestines; however, in individuals with liver disease, endogenous production of ammonia may cause toxicity. Emesis should not be induced in case of ingestion of ammonia, but administration of activated charcoal, gastric lavage, or neutralization with weak acids is recommended HSDB (2003). Elimination of urease-producing enteric bacteria with oral antibiotics decreases the amount of ammonia absorbed from the gut (Gilbert 1988). Because ammonia is readily soluble in water at low concentrations, very little may reach and be absorbed in the lungs. Instead, ammonia at low concentrations may be absorbed in the mucosa of the upper respiratory tract and swallowed. Movement to an area of fresh air as quickly as possible would limit respiratory damage and absorption via the lungs.

3.11.2 Reducing Body Burden

No experimental data regarding methods for reducing the ammonia body burden were located. In healthy people, ammonia is efficiently metabolized via the urea cycle, primarily in the liver, and eliminated in the urine and feces (Fürst et al. 1969; Richards et al. 1975).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The primary effects of ammonia are related to its alkalinity and its solubility in water, which results in rapid and severe tissue damage. It is extremely important to get to an area free of ammonia gas and to remove all clothing contaminated with ammonia as quickly as possible. Skin and eyes should be irrigated with water for at least 15–20 minutes at the time of exposure and periodically for 24 hours after exposure (Millea et al. 1989). Irrigation of the eye should continue until the pH of the conjunctival sac is less than 8.5 (Grant 1974). This should be followed with proper medical treatment for respiratory symptoms and dermal and ocular burns.

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 ammonia 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 ammonia.

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 Ammonia

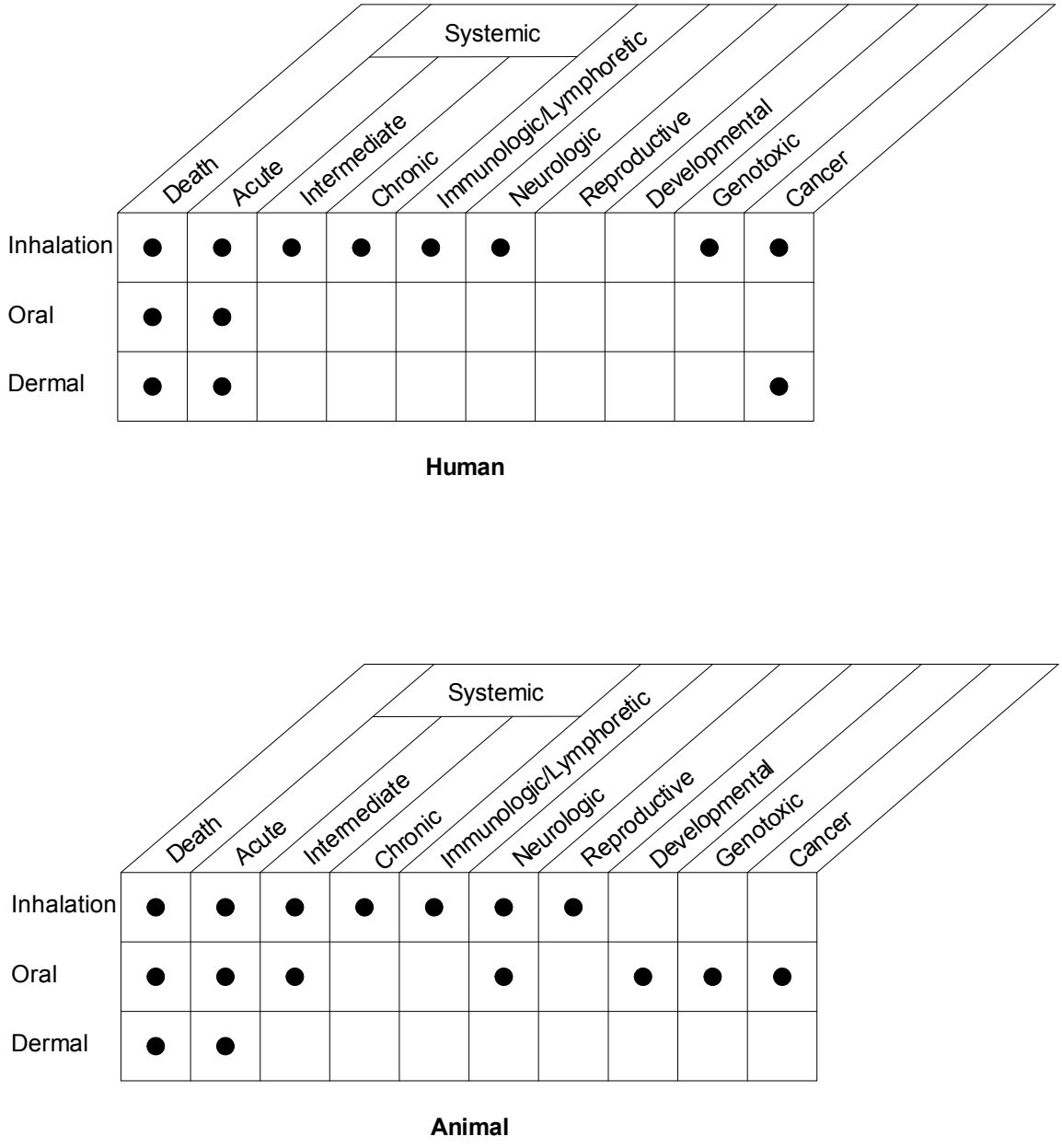
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to ammonia are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of ammonia. Each dot in the figure indicates that one or more 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.

Information regarding health effects of ammonia in humans consists largely of case reports of fatalities or illnesses following massive inhalation and/or dermal exposures resulting from accidental explosions or leakages. A few controlled studies have been conducted on inhalation and oral exposure effects. Health effects of ammonia in animals have been investigated in numerous inhalation studies, and a few oral and dermal exposure studies. Clearly, ammonia is an acutely toxic chemical in high concentrations. As indicated in Figure 3-6, available data address these concerns, both in humans and animals. The data indicate that airway blockage, edema, burns, and lesions of tissues directly exposed to ammonia or NH_4^+ are the most prominent ammonia-related effects. Secondary effects include liver and kidney damage, along with decreased resistance to infection.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. The available human and animal data provide strong evidence that acute-duration exposure to ammonia can result in site-of-contact lesions primarily of the skin, eyes, and respiratory tract. In some cases, exposure to very high ammonia concentrations has resulted in death (Arwood et al. 1985; Walton 1973). Respiratory tract irritation (Burns et al. 1985; Close et al. 1980; Couturier et al. 1971; de la Hoz et al. 1996; Ferguson et al. 1977; George et al. 2000; Hatton et al. 1979; Heifer 1971; Kerstein et al. 2001; Latenser and Lucktong 2000; Leduc et al. 1992; Millea et al. 1989; Morgan 1997; Price et al. 1983; Sekizawa and Tsubone 1994; Sobonya 1977; Taplin et al. 1976; Verberk 1977; Weiser and Mackenroth 1989) and impaired pulmonary function (Kass et al. 1972; Silverman et al. 1949) have been observed in humans acutely exposed to ammonia gas. Animal studies support the

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



identification of the respiratory tract as a sensitive target of toxicity (Coon et al. 1970; Kapeghian et al. 1982; Mayan and Merilan 1972; Richard et al. 1978a, 1978b; Schaerdel et al. 1983; Stombaugh et al. 1969). Nonrespiratory tract effects (e.g., cardiovascular effects, renal effects) have also been observed following inhalation exposure. However, these effects were not consistently observed or may be secondary to the respiratory tract damage. Additional studies would be useful to assess the potential toxicity of NH_4^+ to remote tissues. The available acute data were considered adequate to derive an acute-duration inhalation MRL (Verbeck et al. 1977). No acute-duration oral MRL was derived for NH_4^+. The acute-duration oral database consists of case reports with no dose information (Klein et al. 1985; Klendshoj and Rejent 1966; Lopez et al. 1988) and several animal studies that examined a limited number of end points (Noda and Chikamori 1976), involved a single exposure resulting in no effect, serious effects, or unsupported effects (Benyajati and Goldstein 1975; Koenig and Koenig 1949), and a repeated exposure study that found effects at high dosages (Barzel 1975). In addition, many animal studies have been conducted with ammonium chloride, a substance widely used experimentally to induce metabolic acidosis in animals. Metabolic acidosis is not a consequence of the ammonium ion, but is due to the formation of hydrogen chloride. Metabolic acidosis can affect the lungs, kidney, nervous system, liver, and bone. Ingestion of concentrated ammonia will cause irritation and damage to the mouth, throat, and gastrointestinal tract. Given the levels of ammonia in the environment, such exposure scenario is unlikely. Additional oral exposure studies do not seem warranted at this time. The available data on the dermal toxicity of ammonia suggest that the skin is a sensitive target of toxicity. Cutaneous burns have been reported in humans exposed to ammonia liquid and/or airborne ammonia (Amshel et al. 2000; da Fonseca et al. 1998; George et al. 2000; Kerstein et al. 2001; Latenser and Lucktong 2000; Leduc et al. 1992; Rosenbaum et al. 1998; Weiser and Mackenroth 1989). Ocular effects (inflamed eyes, lacrimation, swelling of the eyelids, transient blindness, blurred vision, and corneal abrasions) have been reported in humans exposed to ammonia (Beare et al. 1988; Caplin 1941; Close et al. 1980; Ferguson et al. 1977; Grant 1974; Hatton et al. 1979; Jarudi and Golden 1973; Kass et al. 1972; Latenser and Lucktong 2000; Legters et al. 1981; Levy et al. 1964; McGuinness 1969; Montague and Macneil 1980; Price et al. 1983; Silverman et al. 1949; Slot 1938; Sobonya 1977; Stombaugh 1969; Stroud 1981; Verberk 1977; Ward et al. 1983; Yang et al. 1987). Additional studies to examine the dermal toxicity of ammonia are unlikely to provide new key information.

Intermediate-Duration Exposure. Information on the toxicity of inhaled ammonia in humans exposed for an intermediate duration is limited to a case report of an individual who developed asthma-like symptoms following exposure to ammonia gas for 5 months (Lee et al. 1993) and a study with volunteers exposed intermittently for 5–6 weeks (Ferguson et al. 1977). The latter study found no

significant changes in pulmonary function in subjects exposed to up to 100 ppm ammonia, but eye and throat irritation occurred at ≥50 ppm. Because some uncertainties regarding the study design and reporting, the Fergusson et al. (1977) study could not be used as basis for an intermediate-duration inhalation MRL. Several animal studies examined the toxicity of ammonia following intermittent or continuous exposure to ammonia. As with acute-duration exposure, these studies suggest that the respiratory tract is the most sensitive target of toxicity. Symptoms of irritation, nasal lesions, dyspnea, and pulmonary inflammation have been observed in several animal species (Broderson et al. 1976; Coon et al. 1970; Drummond et al. 1980; Gaafar et al. 1992; Sjöblom et al. 1999; Stombaugh et al. 1969). In general, the concentrations used in these studies were higher than the lowest adverse effect levels identified for acute-duration exposure. No intermediate-duration oral MRL was derived for some of the same reasons mentioned under acute-duration exposure. No human studies or reports of intermediate-duration oral exposure to NH_4^+ were located. Animal studies have reported decreases in body weight gain in rats exposed via drinking water (Gupta et al. 1979) or diet (Boyano-Adanez et al. 1996). It should be mentioned that Gupta et al. (1979) administered ammonium sulfamate to the rats. Ammonium sulfamate is an herbicide for which there is little toxicity information in the open literature. The EPA (IRIS 2004) has derived an oral RfD for the sulfamate moiety based on the results of Gupta et al. (1979). Following gavage administration of ammonium salts, bone, blood pressure, adrenal gland, and renal effects have been observed in early studies of generally poor quality (Bodansky et al. 1932; Fazekas 1939; Seegal 1927). Additional intermediate-duration oral low to moderate dose studies are unlikely to provide new valuable information. No intermediate-duration dermal exposure studies were identified. Based on the irritant properties of ammonia, it is reasonable to assume that direct contact of the skin with ammonia for a prolonged time will produce irritation.

Chronic-Duration Exposure and Cancer. Several studies have examined the relationship between chronic exposure to ammonia in the air and respiratory effects. Studies of farmers working in enclosed livestock facilities provide evidence that ammonia may contribute to transient respiratory distress (Choudat et al. 1994; Cormier et al. 2000; Donham et al. 1995, 2000; Heederik et al. 1990, 1991; Melbostad and Eduard 2001; Reynolds et al. 1996; Vogelzang et al. 1997, 2000); however, co-exposure to total dust, respirable dust, carbon dioxide, total endotoxins, respirable endotoxins, fungi, bacteria, and/or molds complicates the interpretation of these studies. A study of workers at a fertilizer production facility found an association between respiratory effects and ammonia exposure at levels of ammonia higher than 25 ppm (Ballal et al. 1998). Another long-term study of workers exposed to an average of 9.2 ppm ammonia did not find respiratory effects (Holness et al. 1989). A chronic-duration inhalation MRL was derived based on the findings of Holness et al. (1989). Animal studies examining the chronic

toxicity of inhaled ammonia were not identified. No chronic-duration oral or dermal data were located. A need for such studies is not apparent at this time.

There are limited data to assess the carcinogenic potential of ammonia. Nasal cancer was reported in an individual accidentally exposed to a refrigeration-oil mixture, but the role of ammonia, if any, is unknown (Shimkin et al. 1954). Animal carcinogenicity data consist of several oral exposure studies. Ammonia was not found to increase the occurrence of tumors following oral exposure to relatively low doses (Toth 1972; Uzvolgyi and Bojan 1980). Another study found evidence that ammonia administered as drinking fluid may act as a cancer promoter (Tsujii et al. 1992a, 1995). The dose of ammonia administered can be estimated at 200 mg/day, compared to the estimated 0.36 mg/day from water ingestion for the general population (WHO 1986). The relevance of these studies to exposures in humans is unknown. The available information does not suggest that ammonia is carcinogenic, but well-designed studies in animals have not been conducted and may be warranted.

Genotoxicity. Data on the genotoxicity of ammonia in humans are limited to a study of workers at a fertilizer factory that found an increase in clastogenic effects (Yadav and Kaushik 1997). *In vivo* animal data consist of a study in mice that found alterations in the occurrence of micronuclei (Yadav and Kaushik 1997) and several studies in *D. melanogaster* that resulted in a positive response for mutagenic lethality (Lobasov and Smirnov 1934), but negative responses for sex-linked recessive lethal mutations and dominant lethality (Auerbach and Robson 1947). *In vitro* studies revealed positive responses for genotoxicity in *E. coli* (Demerec et al. 1951), and chick (Rosenfeld 1932) and mouse (Capuco 1977; Visek et al. 1972) fibroblasts. It would be valuable to further assess the genotoxicity of ammonia with mutagenicity assays in *S. typhimurium* and *in vitro* and/or *in vivo* tests for chromosomal aberrations in mammalian systems.

Reproductive Toxicity. No information was located regarding reproductive effects of ammonia in humans. Reproductive toxicity data in animals are limited to a study in pigs exposed prior to mating and until gestation day 30 (Diekman et al. 1993). This study did not find alterations in fetus-to-corpus luteum ratio, number of live fetuses, or ovarian or uterine weights (6 weeks of exposure only). This study is not adequate for assessing reproductive toxicity because very low concentrations were used, there were no unexposed controls, and only females were exposed to ammonia. Additional studies are needed to assess ammonia's potential to induce reproductive effects.

Developmental Toxicity. No information was located regarding developmental effects of ammonia in humans and very limited data were located for animals. No alterations in number of live fetuses or fetal length were observed in a study of pigs exposed to a relatively low concentration of ammonia for 6 weeks prior to mating and until gestation day 30 (Diekman et al. 1993). A reduction in body weight gain was observed in the offspring of rats orally exposed to high doses of ammonia, but no information was provided regarding the health of the dams (Miñana et al. 1995). Developmental toxicity studies are needed to assess the potential of ammonia to damage the developing organism.

Immunotoxicity. Secondary infection has been observed in humans who have received severe burns from exposure to highly concentrated aerosols derived from ammonia (Sobonya 1977; Taplin et al. 1976). It is not known if this represents a primary effect on the immune system in humans since necrosis of exposed tissues facilitates infection by pathogenic organisms. Animal studies have shown that exposure to airborne ammonia may impair immune function (Broderson et al. 1976; Gustin et al. 1994; Richard et al. 1978a; Targowski et al. 1984). No oral immunotoxicity data were located. The available data provide suggestive evidence that ammonia may be an immunotoxicant. It would be valuable to assess the potential for immunotoxicity of ammonia with a battery of immune function tests.

Neurotoxicity. Neurological effects have been observed in humans who received extensive and serious burns from exposure to anhydrous ammonia (George et al. 2000; Hatton et al. 1979; Latenser and Lucktong 2000; White 1971). These effects may be secondary to trauma, rather than direct effects of ammonia on the central nervous system. There are limited data on the potential of NH_4^+ to induce overt neurological effects in animals. A decrease in motor activity has been observed in rodents following an acute exposure to low levels of airborne ammonia (Tepper et al. 1985); no overt signs of neurological impairment were observed following sublethal inhalation exposure (Coon et al. 1970). However, numerous animal studies have found evidence that orally administered ammonia may disrupt normal energy production in the brain and impair neurotransmitter receptors (Bodega et al. 1991; Boyano-Adánez et al. 1996; Kimura and Budka 1986; Kosenko et al. 1993; Kretzschmar et al. 1985; Miñana et al. 1989b; Sobel et al. 1981; Suárez et al. 1992). Additional studies following inhalation and oral exposure would be useful to determine if the neurochemical alterations would result in clinical impairment. No dermal studies examining neurological end points were identified.

Epidemiological and Human Dosimetry Studies. Several studies have examined the toxicity of airborne ammonia in workers (Ballal et al. 1998; Choudat et al. 1994; Cormier et al. 2000; Donham et al. 1995, 2000; Heederik et al. 1990, 1991; Holness et al. 1989; Melbostad and Eduard 2001; Reynolds et al.

1996; Vogelzang et al. 1997, 2000). These studies have primarily focused on the respiratory tract, which is the most sensitive target of toxicity. Interpretation of many of these studies is complicated by co-exposure to other chemicals and microorganisms. In addition to these studies, there are reports of acute-duration exposure to ammonia via inhalation (Burns et al. 1985; Close et al. 1980; Couturier et al. 1971; de la Hoz et al. 1996; Ferguson et al. 1977; George et al. 2000; Hatton et al. 1979; Heifer 1971; Kass et al. 1972; Kerstein et al. 2001; Latenser and Lucktong 2000; Leduc et al. 1992; Millea et al. 1989; Morgan 1997; O'Kane 1983; Price et al. 1983; Sekizawa and Tsubone 1994; Sobonya 1977; Taplin et al. 1976; Verberk 1977; Weiser and Mackenroth 1989), ingestion (Klein et al. 1985; Klendshoj and Rejent 1966; Lopez et al. 1988), dermal contact (Amshel et al. 2000; da Fonseca et al. 1998; George et al. 2000; Kerstein et al. 2001; Latenser and Lucktong 2000; Leduc et al. 1992; Rosenbaum et al. 1998; Weiser and Mackenroth 1989), or ocular contact (Beare et al. 1988; Caplin 1941; Close et al. 1980; Ferguson et al. 1977; Grant 1974; Hatton et al. 1979; Jarudi and Golden 1973; Latenser and Lucktong 2000; Legters et al. 1981; Levy et al. 1964; McGuinness 1969; Montague and Macneil 1980; Price et al. 1983; Silverman et al. 1949; Slot 1938; Sobonya 1977; Stombaugh 1969; Stroud 1981; Verberk 1977; Ward et al. 1983; Yang et al. 1987). These studies suggest that the most sensitive target is the site of contact. The carcinogenic potential of ammonia has not been assessed in humans. There are several subpopulations of individuals exposed to higher than normal levels of ammonia; these groups include farmers and communities living near fertilizer plants. Studies of these groups that involved examination for a variety of potential effects could provide useful information on the toxicity of ammonia in humans. In addition, if the study group included both children and adults, these data would address the issue of age-related differences in toxicity.

Biomarkers of Exposure and Effect.

Exposure. There are no known specific biomarkers of exposure for ammonia in humans or animals. Furthermore, no evidence for alterations in clinical indices of body ammonia or nitrogen levels after exposure to exogenous ammonia has been reported. It does not seem useful at this time to develop biomarkers of exposure for ammonia because after exposure to low levels, ammonia is either rapidly cleared from the body or metabolized to compounds found endogenously at appreciable levels. Exposure to high concentrations is immediately and overtly toxic, which eliminates the need for a more subtle biomarker.

Effect. There are no known specific biomarkers of effect for ammonia in humans or animals. Lesions produced by exposure to high concentrations of ammonia are similar to those produced by other caustic substances.

Absorption, Distribution, Metabolism, and Excretion. Measurement of ammonia absorption is complicated by the appreciable levels of endogenously produced ammonia. Although, most of the inhaled ammonia is retained in the tissues of the upper respiratory tract, inhalation exposure to low levels of ammonia can result in a small amount of absorption (Silverman et al. 1949). As the ammonia concentration increases, the ability of the upper respiratory tract to retain ammonia is saturated, and a larger percentage is absorbed into the blood stream (Silverman et al. 1949). Absorption into the systemic circulation after oral exposure is limited (Metges et al. 1999). Ammonium ions absorbed from the gastrointestinal tract travels via the hepatic portal vein directly to the liver where, in healthy individuals, most of it is converted to urea and glutamine. Although it has not been extensively studied, dermal absorption of ammonia does not occur to a great extent; WHO (1986) concluded that systemic effects from skin and eye exposure to ammonia are not quantitatively important. Data are not available to assess the distribution of ammonia in humans or animals. Studies examining the distribution of ammonia would be useful for identifying potential targets of toxicity. Studies on endogenously produced ammonia, however, indicate that it is distributed to most of the organs and tissues of the body. Extensive work has been completed on the metabolism of ammonia and its participation in the glutamine cycle and the urea cycle (Duda and Handler 1958; Fürst et al. 1969; Richards et al. 1975; Vitti et al. 1964). Data regarding excretion are limited but it is known that ammonia inhaled at low levels is excreted primarily unchanged in the expired breath (Silverman et al. 1949); NH_4^+ absorbed from the gastrointestinal tract is excreted primarily in the urine as urea and other urinary nitrogen compounds (Gay et al. 1969; Pitts 1971; Richards et al. 1975; Summerskill and Wolpert 1970). No information regarding excretion after dermal exposure was located.

Comparative Toxicokinetics. Available data indicate that ammonia has similar targets of toxicity in humans and animals. Ammonia is most hazardous as a site-of-contact toxicant; therefore, the respiratory system is most vulnerable after inhalation exposure, the gastrointestinal tract is most vulnerable after oral exposure, and the skin and eyes are most vulnerable after dermal/ocular exposure. Limited human and animal data are available for toxicokinetics; however, these data indicate that humans and animals are probably very similar regarding the toxicokinetic disposition of ammonia. Furthermore, it is reasonable to expect, especially given the biochemical importance of ammonia, that humans and animals would handle this compound similarly.

Methods for Reducing Toxic Effects. There are limited specific data on reducing the toxic effects of ammonia. Many of the methods are generic approaches, such as getting to an area with fresh air and removal of contaminated clothing. No methods were identified for reducing the body burden or interfering with the mechanisms of toxicity. Studies designed to identify methods for interfering with the damage associated with direct contact with ammonia would be useful.

Children's Susceptibility. There are limited data on the toxicity of ammonia in children and no information on effects in adults who were exposed as children. A higher incidence of respiratory diseases was found in school children exposed to airborne ammonia and other chemicals (Gomzi 1999; Gomzi and Šarić 1997). There is no indication that children are more susceptible to the effects of ammonia than adults; studies of children and adults exposed to ammonia would be useful for assessing potential age-related differences in ammonia toxicity.

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

3.12.3 Ongoing Studies

Ongoing studies pertaining to ammonia have been identified and are shown in Table 3-5.

Table 3-5. Ongoing Studies on the Health Effects of Ammonia

Investigator	Affiliation	Research description	Sponsor
Seashore MR	Yale University	Sodium phenylbutyrate treatment of inborn errors of ammonia metabolism	National Center for Research Resources
Wall SM	University of Texas Health Science Center	$NH4^+$ transport in renal inner medullary collecting duct	National Institute of Diabetes and Digestive and Kidney Diseases
Matthews JB	University of Cincinnati	Intestinal secretion and inflammation; impact of ammonia	National Institute of Diabetes and Digestive and Kidney Diseases
Wall SM	University of Texas Health Science Center	Renal net acid secretion and $Na^+/K^+/2Cl$- cotransporter	National Institute of Diabetes and Digestive and Kidney Diseases
Weiner ID	University of Florida	Localization of ammonia transporters in human liver	National Institute of Diabetes and Digestive and Kidney Diseases
Raushel FM	Texas A&M University System	Mechanism and control of urea biosynthesis	National Institute of Diabetes and Digestive and Kidney Diseases
Hammon DS	Utah State University, Animal Dairy and Vet Science	Gamete and embryo toxic effects of ammonium in cattle	Animal Health Award
Nagami GT	Department of Veterans Affairs, Medical Center West Los Angeles, California	Effect of angiotensin II on ammonia production by tubule cells. Effect of acidosis on renin-angiotensin system	Department of Veterans Affairs, Research and Development, Washington, DC
Nagami GT	Department of Veterans Affairs, Medical Center West Los Angeles, California	Ammonia production and transport by the proximal tubule	Department of Veterans Affairs, Research and Development, Washington, DC
Feldman GM	Department of Veterans Affairs, Medical Center Richmond, Virginia	Colonic transport of bicarbonate, ammonium and small organic anions	Department of Veterans Affairs, Research and Development, Washington, DC
Walsch PJ	University of Miami	Mechanism of tolerance of extreme ammonia	National Institute of Environmental Health Sciences
Weiner ID	Department of Veterans Affairs, Medical Center Gainesville, Florida	Effect of ammonia on IMCD H-K-ATPase. Expression of an ammonia-sensitive protein in brain that mediates ammonia's neurological effects	Department of Veterans Affairs, Research and Development, Washington, DC
Sastrasinh S	Department of Veterans Affairs, Medical Center East Orange, New Jersey	Na^+/H^+ antiport in renal mitochondria	Department of Veterans Affairs, Research and Development, Washington, DC

Source: FEDRIP (2003)

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of ammonia are presented in Table 4-1. These data are for ammonia in its pure gaseous state (i.e., anhydrous ammonia). Ammonia is also commercially and commonly available as an aqueous solution; the most common commercial formulation is 28–30% NH_3 (Weast et al. 1988). At this concentration, ammonia forms a nearly saturated solution in water. Data on ammonia in aqueous solution, ammonium hydroxide, and ammonium ion are also included in Table 4-1 where appropriate.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

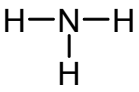
Ammonium hydroxide is a weak base that is partially ionized in water according to the equilibrium:

$$NH_3 + H_20 \quad o \quad [NH_4OH] \quad o \quad NH_4^+ + OH^-$$

The dissociation constant, K_b, is $1.774x10^5$ at 25 °C (pK_b is 4.751) and increases slightly with increasing temperature (Weast et al. 1988). At pH 9.25 half of the ammonia will be un-ionized (NH_3) and half will be ionized (NH_4^+). At pH 8.25 and 7.25, 90, and 99% of the ammonia will be ionized, respectively. Therefore, at most environmentally significant pHs, ammonia will be largely ionized; the fraction of un-ionized ammonia will become increasingly more important at pHs above 7. As a result, many physical and chemical properties will be a function of pH. For example, the solubility of ammonia in water will increase with decreasing pH. The volatility of ammonia increases with increasing pH; therefore, it volatilizes freely from solution at high pH values. Ammonium salts such as chloride, nitrate, and sulfate are strongly dissociated and very soluble in water (Weast et al. 1988); therefore, changes in pH will not normally result in the formation of ammonium precipitates.

The physical and chemical properties of ammonia are presented in Table 4-2. Also included are some chemical and physical properties of ammonia in solution. Ammonia in solution is widely available, and it is often referred to as ammonium hydroxide and has been also historically referred to as “spirit of hartshorn” (Windholz 1983).

Table 4-1. Chemical Identity of Ammonia

Characteristic	Information	Reference
Chemical name	Ammonia	
Synonym(s)	Anhydrous ammonia, AM-FOL, Ammonia gas, Liquid ammonia, Nitro-sil, R 717, Spirit of hartshorn	EPA 1987a; Windholz 1983
Registered trade name(s)	No data	
Chemical formula	NH_3	
Chemical structure		
Identification numbers:		
CAS Registry	7664-41-7	HSDB 2003
NIOSH RTECS	B00875000	NIOSH 2002a
anhydrous ammonia	B00875000	
aqueous solution	B00875000	
aqua ammonia	B00875000	
EPA Hazardous Waste	No data	
OHM/TADS	7216584	OHM-TADS 1988
DOT/UN/NA/IMCO shipping		
anhydrous	UN 1005	NIOSH 2002a
solution (10–35%)	UN 2672	
solution (35–50%)	UN 2073	
solution (>50%)	UN 1005	
HSDB	162	HSDB 2003
NCI	No data	

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

Table 4-2. Physical and Chemical Properties of Ammonia

Property	Value	Reference
Molecular weight	17.03	LeBlanc et al. 1978
Color	Colorless	LeBlanc et al. 1978
Physical state	Gas at room temperature	LeBlanc et al. 1978
Melting point	-77.7 °C	LeBlanc et al. 1978
Boiling point	-33.35 °C	LeBlanc et al. 1978
Density:		
Gas	0.7710 g/L	Weast et al. 1988
Aqueous solution (28%)	0.89801 (20 °C) g/L	Windholz 1983
Liquid	0.6818 g/L (-33.35 °C, 1 atm)	Windholz 1983
Vapor density	0.5967 (air=1)	Windholz 1983
Specific gravity (25 °C)	0.747 g/L	Lide 1998
Odor	Sharp, intensely irritating	Sax and Lewis 1987
Odor threshold:		
Air	25 ppm (18 mg/m^3)	Amoore and Hautala 1983
	48 ppm (34 mg/m^3)	Leonardos et al. 1969
	53 ppm (38 mg/m^3)	Budavari et al. 1996
Water	1.5 ppm	Amoore and Hautala 1983
pKa	9.25 (25°C)	Lide 1998
Solubility:		
Water		
at 0 °C	42.8% (w/w)	LeBlanc et al. 1978
	47% (w/w)	Budavari et al. 1996
at 15 °C	38% (w/w)	Budavari et al. 1996
at 20 °C	33.1% (w/w)	LeBlanc et al. 1978
	34% (w/w)	Budavari et al. 1996
at 25 °C	34% (w/w)	LeBlanc et al. 1978
	31% (w/w)	Budavari et al. 1996
at 30 °C	28% (w/w)	Budavari et al. 1996
at 50 °C	18% (w/w)	Budavari et al. 1996
Organic solvent(s)		
at 0 °C	20% (w/w) in absolute ethanol	Budavari et al. 1996
at 25 °C	10% (w/w) in absolute ethanol	Budavari et al. 1996
	16% (w/w) in methanol	Budavari et al. 1996
	Soluble in chloroform and ether	Budavari et al. 1996
Partition coefficients:		
Log K_{ow}	0.23 (estimated)	EPIWIN 2000

Table 4-2. Physical and Chemical Properties of Ammonia

Property	Value	Reference
Log K_{oc}	1.155 (estimated)	EPIWIN 2000
Vapor pressure:		
Anhydrous NH_3	8.5 atm (20 °C)	Sax and Lewis 1987
	10.2 atm (25 °C)	Daubert and Danner 1989
Aqueous NH_3 (28%)	2.9 atm (25 °C)	Daubert and Danner 1989
Henry's law constant	1.6×10^{-5} atm-m^3/mol (25 °C)	Betterton 1992
	7.3×10^{-6} atm-m^3/mol (pH 7, 23.4 °C)[a]	Ayers et al. 1985
	1.60×10^{-5} atm-m^3/mol (25 °C)[b]	Yoo et al. 1986
	5.01×10^{-6} atm-m^3/mol (5 °C)	Brimblecombe and Dawson 1984
Autoignition temperature	650 °C	LeBlanc et al. 1978
Flashpoint	Not available	
Flammability limits in air	16–25%	LeBlanc et al. 1978
Conversion factors		
ppm (v/v) to mg/m^3 in air (20 °C)	1 ppm (v/v) = 0.707 mg/m^3	Verschueren 1983
mg/m^3 to ppm (v/v) in air (20 °C)	1 mg/m^3 = 1.414 ppm (v/v)	
pH in water	11.6 (1 N)	Windholz 1983
	11.1 (0.1 N)	
	10.6 (0.01 N)	
Explosive limits	Not available	

[a]Unitless constant extrapolated from cited data.
[b]Unconverted value of 0.0168 kg-atm/mol was calculated from equation in citation.

pKa = The dissociation constant of the conjugate acid

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

5.1 PRODUCTION

Ammonia is both a natural and a manufactured chemical. It is a key intermediate in the nitrogen cycle in nature, and microbial production is a major source of ammonia in the world. Recent reports, however, have emphasized the significant influence that humans are having on the global nitrogen budget. At the beginning of the 20th century, most nitrogen was fixed into usable forms (e.g., NH_3) by lightning strikes and microbial nitrogen fixation, with an estimated 90–130 teragrams (Tg; 1 teragram is equivalent to one million metric tons) fixed per year. Human production of fixed nitrogen (NH_3) is now estimated to be 140 Tg N per year, an amount that is similar to non-anthropogenic sources (NSF 1999; Socolow 1999). This increase in human-related ammonia emissions is considerably higher than earlier estimates of the total annual commercial production of ammonia, wherein the anthropogenic emission of ammonia represented approximately 1–5% of nature's global ammonia emission budget (ApSimon et al. 1987; Buijsman et al. 1987; Crutzen 1983; Galbally 1985; Rosswall 1981; Socolow 1999).

The largest amount of naturally produced ammonia is thought to arise from soil. Ammonia from decomposing animal excreta probably accounts for the largest proportion of the ammonia produced, with the decay of organic materials from plants, dead animals, and the like contributing significant amounts (Crutzen 1983; Dawson 1977; Dawson and Farmer 1984; Galbally 1985; Irwin and Williams 1988).

Manufacture of ammonia within the United States has declined steadily over the past several years, with one of the outcomes being the closure of several production plants. The U.S. annual commercial production capacity for ammonia was 16.6 million metric tons in 1999 (CMR 1999), 15.7 million metric tons in 2000 (SRI 2000), but only 9.5 million metric tons in 2001 (Kramer 2002). Production levels increased slightly to 10.8 million metric tons in 2002 (Kramer 2003). High natural gas costs, along with weather-related decreases in demands, contributed to the lower production output in the years leading up to 2002. However, natural gas prices became lower in 2002, and ammonia production increased that year. In 1999, four plant closings eliminated a combined production capacity of 1.2 million tons, some of which was replaced by new facilities (CMR 1999). In 2000, an additional seven plants were completely shut down, and five plants were partially closed due to market conditions (Kramer 2000). In 2002, the largest producer of ammonia in the United States filed for Chapter 11 bankruptcy, leading to the

permanent closing of three large production plants (with a combined production capacity of just over 980,000 metric tons) (Kramer 2003).

While ammonia production decreased over the past few years and some ammonia plants were closed, the states and companies that have historically produced most of the ammonia remained relatively constant. In 2000, 2001, and 2002, Louisiana, Oklahoma, and Texas were the three major producing states, contributing over 50% of the total U.S. ammonia production. Six companies (Farmland Industries Inc., Terra Industries Inc., PCS Nitrogen Inc., Agrium Inc., CF Industries Inc., and Koch Nitrogen) produced 73% of the nation's ammonia in 2002 (Kramer 2003).

There are 2,338 facilities that manufacture or process ammonia in the United States (Table 5-1). The amounts manufactured or processed range from relatively small production activities (from 0 to 99,999 pounds) in Hawaii to very large formulation and processing activities (up to 499,999,999 pounds) in Alaska, Florida, Iowa, Kansas, Louisiana, Nebraska, and Texas (TRI01 2003). As mentioned previously, three states, Louisiana, Oklahoma, and Texas, produce more than 50% of the nation's total NH_3 output.

The major method for commercial production of anhydrous ammonia is a modified Haber-Bosch process. This process was first demonstrated in 1909 (Kramer 2000), and was commercially developed in 1913 in Germany. The first U.S. plant to use this process was built in Syracuse, New York, in 1921 (DOI 1985). The basic Haber-Bosch methodology was still responsible for 98% of the industrially produced ammonia in the United States in 1979 (EPA 1980; HSDB 2003). In this process, nitrogen (obtained from the atmosphere) and hydrogen (obtained from natural gas) are mixed together in a 1 to 3 ratio and passed over a catalyst at high pressure and high temperature. The ammonia thus produced is collected by various means, and any unreacted feed gases are recirculated through the reactor.

Small amounts of ammonia are produced industrially as a by-product of the coking of coal. The largest proportion of industrial ammonia production occurs in areas where natural gas is cheap and plentiful because ammonia is synthesized using natural gas. Large pipelines stretching from Louisiana to Nebraska and from Texas to Minnesota carry anhydrous ammonia from its site of production to agricultural areas where it is used as fertilizer (LeBlanc et al. 1978). These pipelines are capable of transporting or storing 3 million metric tons of ammonia per year, and have a storage capacity of 1.5 million metric tons (Kramer 2000, 2003). Ammonia can also be shipped in large refrigerated, low

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	6	1,000	499,999,999	1, 3, 4, 5, 6, 10, 11, 12
AL	69	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13
AR	45	100	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AS	1	10,000	99,999	11
AZ	16	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
CA	161	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	15	0	999,999	1, 5, 6, 7, 9, 11, 12
CT	24	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12
DC	2	100,000	999,999	12
DE	14	0	999,999	1, 3, 5, 6, 7, 11, 12
FL	54	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
GA	87	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
HI	6	0	99,999	1, 3, 5, 6, 10, 12, 13, 14
IA	54	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
ID	16	100	49,999,999	1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13
IL	108	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
IN	72	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
KS	36	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14
KY	34	100	9,999,999	1, 2, 3, 5, 6, 7, 9, 10, 11, 12, 13, 14
LA	73	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 10, 11, 12, 13, 14
MA	34	0	999,999	1, 2, 3, 5, 6, 7, 10, 11, 12
MD	16	1,000	999,999	1, 3, 5, 6, 7, 8, 10, 11, 12, 13, 14
ME	13	0	999,999	1, 2, 3, 5, 6, 10, 11, 12, 13
MI	72	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13, 14
MN	39	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
MO	50	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
MS	44	100	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MT	12	0	9,999,999	1, 3, 5, 6, 10, 11, 12
NC	86	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
ND	7	0	999,999	1, 3, 5, 6, 10, 11, 12
NE	35	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
NH	14	0	9,999,999	1, 3, 4, 5, 6, 7, 10, 11, 12
NJ	58	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
NM	6	100	99,999	1, 5, 7, 11, 12
NV	11	100	9,999,999	1, 2, 3, 4, 5, 6, 10, 11, 12, 13
NY	63	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OH	123	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	26	100	99,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
OR	46	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
PA	108	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
PR	15	100	999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12
RI	13	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12
SC	64	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
SD	4	1,000	999,999	1, 5, 10, 11
TN	56	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	191	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	28	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12
VA	57	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
VI	1	100,000	999,999	1, 2, 3, 5, 6, 10, 12
VT	2	1,000	99,999	1, 5, 11, 12
WA	38	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WI	68	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	33	0	49,999,999	1, 3, 5, 6, 7, 9, 10, 11, 12, 13
WY	12	0	99,999,999	1, 3, 4, 5, 6, 7, 10, 13

Source: TRI01 2003 (Data are from 2001)

[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

pressure tanks (holding between 4 and 30 thousand tons) or smaller (holding approximately 210 tons), pressurized tanks (Farm Chemicals Handbook 1987). Barges are often used for refrigerated shipments because of their lower cost. Ammonia can be stored in refrigerated tanks holding up to 36,000 tons for use in the ammonia market. Smaller amounts of ammonia are stored in pressurized tanks.

The supply of ammonia for domestic uses has been historically met by domestic production. The ability to meet the ammonia demand depends on the amount of crop acres planted, the price of imported fertilizers, the cost of natural gas, and the availability of ammonia via import from abroad. In 2000, 3.9 million metric tons of anhydrous ammonia were imported; in 2001, this amount increased to more than 5.5 million metric tons. In 2000, domestic sources supplied 15.7 million metric tons of ammonia, whereas international sources provided 3.9 million metric tons; imports represented 20% of the total supply. In 2001 by comparison, domestic production dropped to 9.5 million metric tons, while imports increased 5.5 million metric tons; imports in 2001 represented almost 37% of the supply of ammonia (Kramer 2002). The amount of ammonia imported in 2002 held steady—the amount imported was just under 5.7 million metric tons (Kramer 2003)—while domestic production rose slightly to 10.8 million metric tons. Imports in 2002 represented 35% of the domestic need. The increases in imported ammonia, along with decreased domestic production, resulted in a substantial increase in reliance on foreign sources during these 3 years.

5.2 IMPORT/EXPORT

The import and export of ammonia have fluctuated slightly over the last few years. In 2000, the amount of ammonia imported into the United States was slightly less than 3.9 million metric tons. In both 2001 and 2002, the amount of ammonia imported into the United States was slightly more than 5.5 million metric tons (Kramer 2003). These years reflect a 41% increase in the amount of ammonia imported compared to 2000. U.S. exports of ammonia fell during the years following the change in domestic production and import from abroad. Exports in 2000 were approximately 0.66 million metric tons, and in 2001, 0.65 million metric tons were exported. Exports then dropped to 2/3 of those reported in the previous years. In 2002, when domestic production dropped and imports increased, only 0.44 million metric tons of ammonia were exported.

5.3 USE

The largest and most significant use of ammonia and ammonium compounds is the agricultural application of fertilizers. Ammonia and ammonium compounds used as fertilizer represent 89–90% of the commercially produced ammonia, with plastics, synthetic fibers and resins, explosives, and other uses accounting for most of the remainder (Kramer 2002, 2004). Direct uses of ammonia as fertilizer can be broken down into the following categories (percentages based on mass of nitrogen in each compound): anhydrous ammonia, 26%; urea/ammonium nitrate solutions, 23%; urea, 20%; ammonium nitrate, 4.5%; ammonium sulfate, 2%; other forms, 3%; and multiple nutrient forms, 21% (Kramer 2003). Most ammonium compounds and nitric acid, which are produced from anhydrous ammonia, are used directly in the production of fertilizers.

The small proportion of commercially produced ammonia not incorporated into fertilizers is used as a corrosion inhibitor, in the purification of water supplies, as a component of household cleaners, and as a refrigerant. It is also used in the pulp and paper, metallurgy, rubber, food and beverage, textile, and leather industries. Ammonia is used in the manufacture of pharmaceuticals and explosives, and in the production of various chemical intermediates (LeBlanc et al. 1978; Sax and Lewis 1987).

5.4 DISPOSAL

Solutions of ammonia can be highly diluted with water, or alternatively, diluted with water and neutralized with HCl and then routed to the sewer system. The amount released to the receiving stream should not exceed the established limits for ammonia. Limited amounts of gaseous ammonia may be discharged to the atmosphere. Federal, state, and local guidelines should be consulted before disposal.

Disposal of liquefied ammonia or of large quantities of gaseous or aqueous ammonia directly into water is not desirable, because of the large amount of heat generated. This generation of heat could increase exposure to personnel involved in the process. Recovery of ammonia from aqueous waste solutions is a viable option for many industries (HSDB 2003).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Ammonia has been identified in at least 137 of the 1,647 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). However, the number of sites evaluated for ammonia is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 135 are located within the United States and 2 are located in the Commonwealth of Puerto Rico (not shown).

Ammonia is a naturally-occurring compound that is an intermediate in the global nitrogen cycle. It is essential for many biological processes and is a central compound in all living organisms. Nitrogen is converted from atmospheric N_2 to other forms by different processes. Nitrogen fixation (the process of converting atmospheric N_2 to NH_3) occurs naturally due to biological processes. Lightning strikes also "fix" atmospheric nitrogen, but they produce nitrogen oxides, not ammonia. The current amount of nitrogen fixation that occurs by industrial processes equals that of natural, terrestrial nitrogen fixation. Both natural and anthropogenic sources produce a total of approximately 230–270 million metric tons of NH_3 per year.

Because of its role in natural processes and cycles, ammonia is found at low concentrations in most environmental media. When ammonia is found at a local concentration that is higher than these background levels, it is often a result of human influence. Ammonia is hazardous only when exposure is to high levels. In determining the environmental fate of ammonia, several factors should be considered, the primary one being that ammonia is the most abundant alkaline gas in the environment. An acid-base reaction between water and ammonia occurs such that the dominant form of ammonia in water, at environmentally relevant pHs, is the ammonium ion. In media where water is usually present, such as soil, plants, biological tissue, and water itself, ammonia and ammonium are in dynamic equilibrium.

Ammonia is a key intermediate in the nitrogen cycle, a natural cycle that is coupled with other important biological cycles (i.e., the sulfur cycle and carbon cycle). An understanding of the role of ammonia in the nitrogen cycle, at least on a generalized level, is important in determining the environmental fate of ammonia. A simplified schematic of the microbial processes of the nitrogen cycle that involves ammonia can be found in Figure 6-2. Microorganisms perform four processes in the nitrogen cycle that result in

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

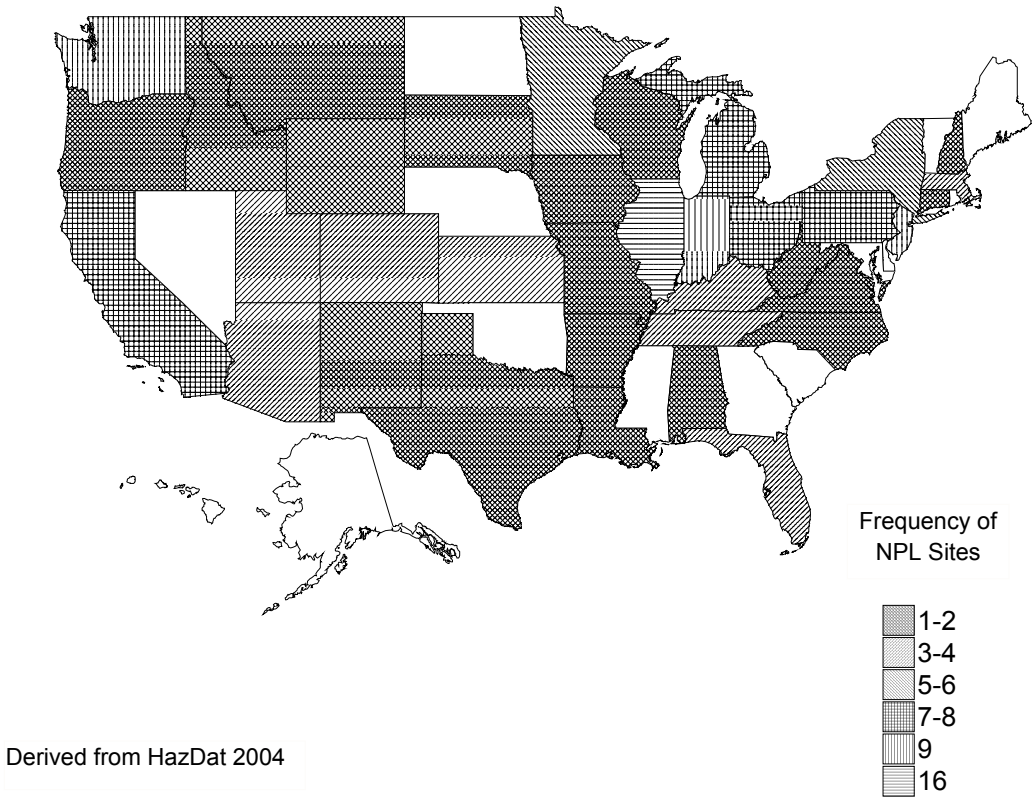
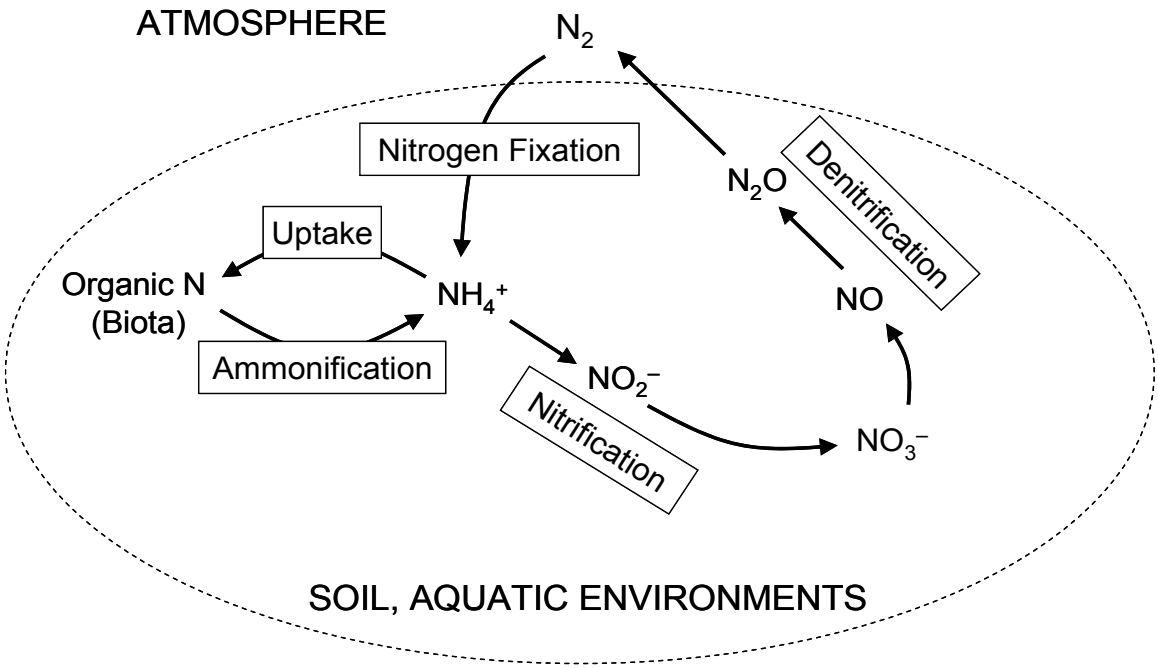


Figure 6-2. Simplified Schematic for the Microbial Processes of the Nitrogen Cycle



production or transformation of ammonia: nitrogen fixation, nitrification, denitrification, and ammonification. As part of this cycle, nitrogen gas and oxidized forms of nitrogen are transformed and returned to the biological world. Nitrogen fixation is the process whereby atmospheric nitrogen gas is converted to ammonia, which is then assimilated into amino acids; it has been found that there is only a small proportion of all genera of microorganisms that can fix nitrogen. Denitrification is the process whereby the nitrogen oxides (i.e., nitrate and nitrite) are reduced under anaerobic conditions to N_2 and N_2O, which can escape to the atmosphere. Nitrification is the biological oxidation of ammoniacal nitrogen to nitrate, with nitrite as the intermediate. Ammonification (or nitrogen mineralization) is the conversion of organic nitrogen into ammonia.

Ammonia may be released to the atmosphere by volatilization from the following sources: decaying organic matter; livestock excreta; fertilizers applied to soils; venting of gas, leaks, or spills during commercial synthesis, production, transportation, or refrigeration equipment failure; sewage or waste water effluent; burning of coal, wood, and other natural products; and volcanic eruptions.

Ammonia may be released to water through effluent from sewage treatment plants, effluent from industrial processes, runoff from fertilized fields, and runoff from areas of concentrated livestock. This usually occurs when the organic N compounds present in these sources enter the water and are converted microbiologically to ammonia.

Ammonia may be released to soils by natural or synthetic fertilizer application, animal (including livestock) excrement degradation, decay of organic material from dead plants and animals, and indirectly from natural fixation of atmospheric nitrogen. In this latter case, ammonia releases can occur following nitrogen fixation by free-living microbes and plants (those that are symbiotic nitrogen-fixing bacteria), which subsequently die and release ammonia (or compounds that are converted to ammonia) to the soils.

In the atmosphere, ammonia can be removed by rain or snow washout. Reactions with acidic substances, such as H_2SO_4, HCl, HNO_3, or N oxides (all produced in high concentrations from anthropogenic activities) produce ammonium aerosols, which can undergo dry or wet deposition. The gas phase reaction of ammonia with photochemically produced hydroxyl radicals is thought to contribute about 10% to the overall atmospheric removal process. The best estimate of the half-life of atmospheric ammonia is a few days.

In water, ammonia volatilizes to the atmosphere, is transformed to other nitrogenous compounds, or may be bound to materials in the water. Volatilization is highly pH-dependent, and can also depend on other factors such as temperature, wind speed, and atmospheric ammonia concentration. Transformation of ammonia in water occurs primarily by the microbial processes of nitrification and to lesser extents, denitrification. Nitrification yields nitrate and nitrite anions; the former species can be responsible for methemoglobinemia in human infants if the contaminated water is ingested. Removal of ammonium from water can also occur by adsorption to sediments or suspended organic material.

In soil, ammonia may either volatilize to the atmosphere, adsorb to particulate matter, or undergo microbial transformation to nitrate or nitrite anions. Uptake by plants can also be a significant fate process. Ammonia at natural concentrations in soil is not believed to have a very long half-life. If ammonia is distributed to soil in large concentrations (e.g., following an application of an ammonia-containing fertilizer), the natural biological transformation processes can be overwhelmed, and the environmental fate of ammonia will become dependent upon the physical and chemical properties of ammonia, until the ammonia concentration returns to background levels.

Occupational exposure to ammonia may occur in industries involved in its synthesis, formulation, processing, transportation, and use. Occupational exposure to ammonia can also occur during the use of an extensive number of cleaning products that contain ammonia. Farmers may be exposed during the application of fertilizers containing anhydrous ammonia or liquid ammonia, or manures high in ammonia. Workers at cattle feedlots, poultry confinement buildings, or other industries that have a high concentration of animals may also be exposed.

Exposure of the general population to elevated levels of ammonia is most commonly from the use of household cleaners that contain ammonia. People who live near farms or who visit farms during the application of fertilizer that contain or release ammonia may also be exposed. People living near cattle feedlots, poultry confinement buildings, or other areas where animal populations are concentrated can also be exposed to ammonia, in addition to other gases generated by putrefaction. Ammonia has been identified at 137 out of 1,647 NPL hazardous waste sites (HazDat 2004).

6.2 RELEASES TO THE ENVIRONMENT

Ammonia is commercially produced for many processes, but most production is for agricultural uses, primarily crop fertilizer. As a result of most it being formulated for agricultural practices, ammonia is

commonly distributed to the environment during its intended use as a crop fertilizer. Release data generated for the Toxics Release Inventory (TRI) (see Table 6-1) provide detailed information regarding environmental releases related to industrial activities, but should be used with caution because only certain types of facilities are required to report, and data from these reports do not represent an exhaustive list of all commercial releases. It should be noted that for ammonia, since it is one of the most widely-used agricultural fertilizer chemicals in the United States, the TRI data represent only a small fraction of the environmental release, and do not include releases that occur during farming or other agriculture practices.

Table 6-1 shows the 2001 TRI releases of ammonia from manufacturing or processing facilities to different environmental compartments. Most of the ammonia released to the environment from these facilities was the result of air releases, followed by releases via underground injection. The greatest air releases occurred in the state of Louisiana (12,304,532 pounds), which was almost 2 million more pounds released than the second highest releasing state, Ohio (10,505,480 pounds). Texas released the most ammonia via underground injection (15,014,490 pounds), which was more than 3 times the second highest releasing state, Louisiana (4,446,211 pounds). For all on-site releases, the two states releasing the most ammonia were the adjacent states of Louisiana and Texas (Louisiana released 17,742,736 pounds and Texas released 21,354,611 pounds).

Release of ammonia from production and processing facilities has changed from year to year, with amounts generally decreasing since the early 1990s. Reported air releases have ranged from a high of 254,542,289 pounds in 1989 to a low of 122,057,546 pounds in 2001. Surface water releases have ranged from a high of 48,138,279 pounds in 1990 to a low of 6,621,166 pounds in 2001. Land releases (surface releases) have shown a similar trend, with the highest amount (17,782,641 pounds) released in 1990, and the lowest amount (2,868,728 pounds) released in 1999. The general trend is that less and less ammonia has been released to the environment each year, such that the total amount released in 2001 (158,521,046 pounds) was less than a third of the amount released in 1990 (548,828,735 pounds).

The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

In addition to releases related to agricultural or other anthropogenic usage, ammonia has been identified in several environmental compartments including surface water, groundwater, soil, and sediment collected at 135 of the 1,647 current or former NPL hazardous waste sites in the United States, and in

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

State[c]	Number of facilities	Reported amounts released in pounds per year[b]						
		Air[d]	Water	Under-ground injection	Land	Total on-site release[e]	Total off-site release[f]	Total on and off-site release
AK	7	1,427,011	32,428	5	95,950	1,555,394	0	1,555,394
AL	75	3,192,615	180,703	0	57,288	3,430,606	145,305	3,575,911
AR	48	3,672,621	209,122	0	372	3,882,115	18,078	3,900,193
AS	1	6,920	No data	0	0	6,920	0	6,920
AZ	18	107,967	5	0	260	108,232	350	108,582
CA	178	6,362,240	37,470	41,236	264,004	6,704,950	18,728	6,723,678
CO	19	291,922	12,899	0	4,019	308,840	148	308,988
CT	28	169,071	10,035	0	0	179,106	8	179,114
DC	2	0	487	0	0	487	0	487
DE	14	109,356	3,804	0	7,937	121,097	0	121,097
FL	72	5,646,496	148,226	293,106	124,914	6,212,742	122,755	6,335,497
GA	95	8,291,371	171,670	0	13,140	8,476,181	154,582	8,630,763
HI	7	47,492	660	2,059	30,368	80,579	0	80,579
IA	60	4,686,900	133,403	0	3,829	4,824,132	166,223	4,990,355
ID	16	2,705,639	5,874	0	182,369	2,893,882	21,731	2,915,613
IL	136	2,366,356	56,440	0	68,423	2,491,219	1,108,621	3,599,840
IN	82	1,294,431	55,681	824,984	61,545	2,236,641	23,002	2,259,643
KS	38	3,285,064	36,461	22,555	270,459	3,614,539	42,129	3,656,668
KY	40	1,218,869	83,020	0	4,000	1,305,889	1,483	1,307,372
LA	78	12,304,532	917,883	4,446,211	4,816	17,673,442	69,294	17,742,736
MA	48	591,589	6	0	0	591,595	33,235	624,830
MD	17	482,934	25,246	0	18,569	526,749	4,587	531,336
ME	15	813,198	39,047	0	0	852,245	0	852,245
MI	81	1,579,680	141,346	40,307	68,851	1,830,184	12,981	1,843,165
MN	56	1,790,288	43,283	0	36,315	1,869,886	3,315	1,873,201
MO	55	548,485	319,685	0	11,624	879,794	34,796	914,590
MS	49	4,452,540	394,837	0	46,552	4,893,929	255	4,894,184
MT	14	543,332	10,920	0	9,685	563,937	0	563,937
NC	101	3,054,435	287,555	0	30,750	3,372,740	18,711	3,391,451
ND	9	305,283	17,106	0	88,654	411,043	340	411,383
NE	38	804,872	245,587	0	377,539	1,427,998	243,327	1,671,325
NH	15	128,420	551	0	0	128,971	966	129,937
NJ	67	1,144,702	165,642	0	0	1,310,344	18,406	1,328,750
NM	5	9,780	5	29,497	670	39,952	0	39,952
NV	13	428,880	2,710	0	311,810	743,400	0	743,400
NY	71	1,387,982	61,780	0	8,266	1,458,028	1,540	1,459,568

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

		Reported amounts released in pounds per year[b]						
State[c]	Number of facilities	Air[d]	Water	Under-ground injection	Land	Total on-site release[e]	Total off-site release[f]	Total on and off-site release
OH	136	10,505,480	98,996	2,006,500	52,964	12,663,940	93,861	12,757,801
OK	28	5,995,915	81,112	0	25,716	6,102,743	1,850	6,104,593
OR	51	1,769,989	43,747	0	106,233	1,919,969	1,882	1,921,851
PA	131	2,346,403	229,268	0	13,469	2,589,140	23,359	2,612,499
PR	16	1,938,727	306	0	0	1,939,033	600	1,939,633
RI	22	84,982	3,573	0	0	88,555	0	88,555
SC	68	2,559,694	162,782	0	39,741	2,762,217	5,627	2,767,844
SD	9	86,361	684	0	225	87,270	29,223	116,493
TN	58	4,865,087	487,650	0	796	5,353,533	78,192	5,431,725
TX	209	5,206,675	518,396	15,014,390	199,710	20,939,171	415,440	21,354,611
UT	29	458,197	8,800	0	911,305	1,378,302	503	1,378,805
VA	64	7,866,819	93,001	0	35,707	7,995,527	129,614	8,125,141
VI	1	77,675	42,154	0	0	119,829	0	119,829
VT	2	47,582	4,450	0	0	52,032	0	52,032
WA	45	857,165	137,956	0	22,488	1,017,609	80,200	1,097,809
WI	83	589,027	89,624	0	3,107	681,758	78,850	760,608
WV	36	961,276	758,661	14,387	0	1,734,324	42,951	1,777,275
WY	12	587,219	8,429	239,000	6,610	841,258	0	841,258
Total	2,668	122,057,546	6,621,166	22,974,237	3,621,049	155,273,998	3,247,048	158,521,046

Source: TRI01 2003 (Data are from 2001)

[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]The sum of fugitive and stack releases are included in releases to air by a given facility.
[e]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[f]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

groundwater and soil samples at 2 sites in Puerto Rico (HazDat 2004). Furthermore, ammonia is a key intermediate in nature's nitrogen cycle, and considerable amounts are released to the environment as a result of natural processes. As a result of inputs from natural sources and from anthropogenic sources, ammonia concentrations in nature are in dynamic equilibrium. When ammonia is found at elevated concentrations, however, it is usually a result of anthropogenic activity.

6.2.1 Air

Large amounts of ammonia are released to the atmosphere worldwide by domesticated farm animals (ApSimon et al. 1987; Asman and Janssen 1987; Buijsman et al. 1987; Kramer 2000, 2002; Ryden et al. 1987). Ammonia emissions due to the decay of livestock manure are a source for ammonia release in areas that have artificially high concentrations of animals, such as cattle feedlots and poultry-confinement buildings (Brinson et al. 1994; Hutchinson et al. 1982; Langland 1992; Liao and Bundy 1995; Olivier et al. 1998; Sunesson et al. 2001). In Germany, over 90% of the measured NH_3 emissions originated from agricultural sources (Strogies and Kallweit 1996). In Russia, estimated NH_3 emissions from fertilizer applications and livestock sources accounted for 94% of the total NH_3 emissions from all anthropogenic sources (Tsibulski et al. 1996). The use of high nitrogen content feed for farm animals and the trend toward larger feedlots have been responsible for increased emissions in developed countries.

The application of fertilizer to soil, as ammonia, ammonium compounds, or ammonia precursors (such as urea), is a well documented source of ammonia release to the atmosphere (ApSimon et al. 1987; Beyrouty et al. 1988; Buijsman et al. 1987; Kucey 1988; Olivier et al. 1998; Reynolds and Wolf 1988). The rate of ammonia emission from ground sources, such as freshly fertilized fields and cattle feedlots, is dependent on variables such as the pH, temperature, soil characteristics, rainfall, method of application, wind speed, etc. (Bouwmeester and Vlek 1981; Brunke et al. 1988; Denmead et al. 1982; Hoff et al. 1981; Kucey 1988; Nason et al. 1988; Reynolds and Wolf 1988). Ammonia can volatilize from sewage sludge that has been spread on the surface of the soil (Beauchamp et al. 1978; Ryan and Keeney 1975) as well as from poultry litter (Brinson et al. 1994). In the latter case, composted poultry litter released far less volatile NH_3 to the atmosphere (0–0.24% of applied) than did fresh poultry litter (17–23%) (Brinson et al. 1994). In contrast, the crops themselves are often minor sources of atmospheric NH_3. Harper and Sharpe (1995) demonstrated almost no net atmospheric NH_3 flux in corn crops, due to their relatively similar emission and uptake rates of NH_3 over the growing season.

For much of the history of the Earth, biological activity in soil and natural waters was the primary global source of atmospheric ammonia (Dawson 1977; Dawson and Farmer 1984; National Science Foundation 1999), but this has changed over the last century. Crutzen (1983) suggested that the decay of organic material arising from dead plant, animal, and microbial biomass generates most of the atmospheric ammonia, while Galbally (1985) and Irwin and Williams (1988) suggested that domestic-animal excretions represent the dominant source of atmospheric ammonia. Lee et al. (1997) estimated that grasslands contributed 40% of the total global NH_3 emissions, with domestic animal wastes contributing 42.3% of that. Recent studies, however, provided fairly uniform estimates of ~40% of global NH_3 emissions being due to excreta from domestic animals (Asman et al. 1998; Bouwman et al. 1997; Olivier et al. 1998). Current measurements and estimates, however, indicate that the amount of ammonia produced as a result of anthropogenic activities is equivalent to the amount produced by natural processes (National Science Foundation 1999).

In addition to livestock-related releases, ammonia can be released to the atmosphere through the venting of gases during the production, storage, and transportation of ammonia, and during its formulation or incorporation into secondary products (Buijsman et al. 1987). Long pipelines are used to transport ammonia from its site of manufacture to agricultural areas where it is used as fertilizer (Farm Chemicals Handbook 1987; Kramer 2000; LeBlanc et al. 1978). Releases to the atmosphere could occur at pumping stations and points of transfer along these pipelines, or from leaks. Large refrigerated tanks are used to store ammonia, and release to the environment can occur while venting the pressure in these tanks, or from leaks.

Ammonia can also enter the atmosphere by volatilization from the waste water of industrial processes that involve its production or use, and from the volatilization from the effluent of waste water treatment plants (Buijsman et al. 1987; Langland 1992; Roy and Poricha 1982; Wilkin and Flemal 1980). Ammonia has been found in the exhaust of automobile and diesel engines (Asman et al. 1998; Plerson and Brachaczek 1983). Release to the atmosphere can occur during the burning of coal (Bauer and Andren 1985; Olivier et al. 1998). The latter process, however, is not thought to account for a significant proportion of the total anthropogenic ammonia released to the atmosphere (Olivier et al. 1998; Strogies and Kallweit 1996).

Natural sources of ammonia emissions to the atmosphere are volcanic eruptions, forest fires, and the decomposition of nitrogenous compounds arising from microbially-fixed nitrogen (Galbally 1985; Hegg et al. 1987; National Science Foundation 1999). Excreta from household pets, wild animals, and humans are also contributing sources (Asman and Drukker 1988; Buijsman et al. 1987; Crutzen 1983).

6.2.2 Water

The major point source of release to surface waters is from the effluents of waste water-treatment plants (Barica 1990; Crumpton and Isenhart 1988; Wilkin and Flemal 1980). Ammonia can enter surface waters through the effluent of commercial processes in which ammonia is used or produced (Effler et al. 2001; Huddleston et al. 2000; Matthews et al. 2000; Roy and Poricha 1982). Runoff from fertilized farmland and from areas of concentrated livestock production can also result in the transfer of ammonia to surface water (Corsi et al. 2000; Jingsheng et al. 2000; Wilkin and Flemal 1980). Surface water can absorb ammonia directly from the atmosphere near cattle feedlots, areas where the local atmospheric concentration may be high (Fangmeier et al. 1994; Hutchinson and Viets 1969). Ammonium can also be released to water when N_2-fixing cyanobacteria (also called blue-green algae) die and are decomposed.

6.2.3 Soil

Ammonia enters soil through different processes, primarily human practices (e.g., fertilizer applications, animal husbandry), and natural biological processes. Direct application of fertilizers represents a major influx of ammonia into soils. Of the total U.S. production of anhydrous ammonia, 30% is applied directly to the soil under pressure (Kramer 2000). Approximately 80% of the U.S. production of ammonia is applied to soil in fertilizer formulations designed to release ammoniacal nitrogen. Application of natural fertilizers obtained from livestock excreta will also result in the release of ammonia to the soil (Asman et al. 1998; Beauchamp et al. 1982; Hoff et al. 1981; Olivier et al. 1998). High levels of ammonia in soils can result from the decomposition of animal wastes on cattle feedlots or other confinement areas, as well as from the land disposal of livestock and poultry waste. Ammonia in soil can also arise from the decay of organic material arising from plant, animal, and microbial byproducts and biomass (Dawson 1977; Dawson and Farmer 1984). Microbial fixation of nitrogen from the atmosphere is a natural and continual source of ammonia in soil, which can be released to soil after the microorganisms die (Galbally 1985; National Science Foundation 1999).

In nature, there are many pathways for incorporation of ammonia into soil. Natural sources include microbial decomposition of dead plants and animals, and hydrolysis or breakdown of urea and nitrogenous waste products in animal excretions. Several species of microorganisms can produce ammonia by the fixation of N_2, and these organisms are widely dispersed throughout the soil (Atlas and

Bartha 1998; Crutzen 1983); ammonia is released to the soil only after these microorganisms die. While several species of microbes can perform nitrogen fixation, this capability would not be one that is considered common for most microorganisms.

6.3 ENVIRONMENTAL FATE

In considering the environmental fate of ammonia, it is necessary to emphasize that ammonia is very important in nature and in nature's biological cycles. In our limited understanding of fluxes between these cycles, ammonia is considered a key intermediate. Nature has incorporated many mechanisms and "rules" for altering the distribution of ammonia through the biological system, as circumstances dictate. An in-depth discussion of these phenomena is outside the scope of this document; however, it is important to understand that for ammonia, all organisms contribute, either directly or indirectly, to the direction and distribution of the various environmental-fate processes.

An important consideration that affects the transport and partitioning of ammonia in the environment is that ammonia is a base. As a base, the physical and chemical properties of ammonia are pH-dependent, and thus, environmental-fate processes that influence the transport and partitioning of NH_3 will also be pH-dependent. For some environmental fate processes, a change in pH may only affect the relative rate of a process, while for others, it could change the direction or overall result of that process. The influence of pH on the environmental fate of ammonia will be discussed where appropriate. Temperature is also an important consideration in the environmental fate of ammonia. Temperature, although to a lesser extent than pH, affects the ammonia-ammonium equilibrium.

6.3.1 Transport and Partitioning

Atmospheric ammonia can be readily removed from the air by rain or snow washout (Adamowicz 1979; Asman et al. 1998; Kumar 1985). It can dissolve in the water found in clouds (Asman et al. 1998; Brimblecombe and Dawson 1984; Sprenger and Bachmann 1987) or fog (Johnson et al. 1987). Ammonia can be removed from the atmosphere through the direct absorption by surface waters in areas where the local atmospheric concentration is high (Hutchinson and Viets 1969) and by wet deposition onto soils and surface waters (Asman et al. 1998; Cuesta-Santos et al. 1998; Goulding et al. 1998). Uptake of atmospheric ammonia by different species of plants also occurs (Harper and Sharpe 1995; Nason et al. 1988; Rogers and Aneja 1980). Depending on the local atmospheric concentration, however, plants can

also release ammonia to the atmosphere (Harper and Sharpe 1995; Lee et al. 1997; O'Deen and Porter 1986; Parton et al. 1988). By use of $^{15}NH_3$, it has been demonstrated that minerals and dry soil can rapidly and effectively adsorb NH_3 from air containing trace quantities of this gas (Bremner 1965). Ammonia is the predominant basic gas in the atmosphere (Allen et al. 1989). As such, it is capable of rapidly reacting with atmospheric H_2SO_4, HNO_3, or HCl, forming ammonium aerosols, which can then undergo dry deposition (Allen et al. 1989; Irwin and Williams 1988).

If released to surface water, ammonia can volatilize to the atmosphere or be taken up by aquatic plants. The rate of volatilization of ammonia from water will increase with increasing pH (generally only important above pH values of ~7.0) and temperature, and can be influenced by other environmental factors. Gaseous or liquid ammonia added to water will increase the pH of the medium; the rate of volatilization may increase dramatically if large amounts are released to relatively small static bodies of water, such as rice paddies (DeDatta 1995). Agitation will also increase the rate of volatilization. Georgii and Gravenhorst (1977) calculated the equilibrium concentration of ammonia above the Pacific Ocean. Using a constant concentration of 3 pmol/L, the ammonia concentration above the ocean as a result of increased volatilization was calculated to change from approximately 2.8 to 7 ppb as the pH was increased from 8.1 to 8.4 (at 25 °C). Volatilization of ammonia from flooded rice paddies was found to increase with increasing ammoniacal nitrogen concentration, pH, temperature, and wind velocity (Bouwmeester and Vlek 1981; DeDatta 1995; Tian et al. 2001). Ammonia can also be taken up by aquatic plants as a source of nutrients (Kemp and Dodds 2002).

In water, adsorption of ammonia to sediment and suspended organic material can be important under proper conditions (Ankley et al. 1990). Adsorption to sediment should increase with increasing organic content, increased metal ion content, and decreasing pH. Ammonia, however, can be produced in, and subsequently released from, sediment (Jones et al. 1982; Malcolm et al. 1986).

The uptake of ammonia by fish can also occur under the proper conditions (Hargreaves 1998; Mitz and Giesy 1985). Ammonia is the final breakdown product of nitrogenous-compound metabolism for catfish, and it is normally released through the gills into the surrounding water, driven by a concentration gradient. If the water concentration is abnormally high, the direction of passive ammonia transport is reversed.

A complete discussion of the factors influencing the transport and partitioning of ammonia in soil is outside the scope of this document. Adsorption of ammonia occurs in most moist or dry soils, and

ammonia is predominantly, but not exclusively, held as the ammonium ion. Generally, adsorption will increase with increasing organic-matter content of the soil, and will decrease with increasing pH. Other factors that influence the adsorption of ammonia to soil are the presence of metallic ions, the predominant microbial populations and communities present, and its rate of uptake by plants. The ammonia concentration, temperature, and wind speed can also subtly affect the adsorption process by influencing the rate of volatilization (Bouwman et al. 1997; Bouwmeester and Vlek 1981; Brunke et al. 1988; Denmead et al. 1982; Galbally 1985; Goulding et al. 1998; Hoff et al. 1981; Kucey 1988; Nason et al. 1988; Reynolds and Wolf 1988; Socolow 1999). To demonstrate the influence of pH on the volatilization of ammonia (which, as indicated above, influences the potential for ammonia adsorption), ammonia loss was measured in greenhouse experiments using soils that had been adjusted to different pH values. Following the application of manure to the soil surface, ammonia volatilization was found to be 14% of the applied ammonium at a soil pH of 6.4 (manure pH=6.4). At a soil pH of 7.0 (manure pH=7.8), 65% was lost by volatilization (Hoff et al. 1981). In a study of the effects of SO_2 deposition on soils, it was found that the threshold pH at which ammonia volatilization from soil was drastically reduced did not occur until the pH was reduced to between pH 3.5 and 4.0 (Mahendrappa 1982). This is a relatively unrealistic and unrepresentative pH value for most soils; the results, however, indicate that volatilization will be an important process that affects the transport and partitioning of ammonia in most soils.

Because ammonia, as ammonium ion, is the nutrient of choice for many plants (Kramer 2000; Rosswall 1981), uptake of soil ammonia by living plants is an important fate process. The rate of uptake by plants varies with the growing season. At normal environmental concentrations, ammonia does not have a very long residence time in soil. It is either rapidly taken up by plants, bioconverted by the microbial population, or volatilized to the atmosphere. Because of these processes, and because ammonia generally exists in soils as NH_4^+ (which binds to soils particles), ammonia does not leach readily through soil; thus, it is rarely found as a contaminant of groundwater (Barry et al. 1993). In soil, ammonia that results from the application of fertilizers is usually found in the top 10 inches of the soil (Beauchamp et al. 1982). However, nitrate derived from ammonia may leach to groundwater.

6.3.2 Transformation and Degradation

6.3.2.1 Air

In air, a dominant fate process for ammonia is the reaction with acid air pollutants. Formation of particulate NH_4^+ compounds by reactions with HNO_3 and H_2SO_4 is rapid (Bouwman et al. 1997; Irwin

and Williams 1988). The extent to which this process serves as a removal mechanism depends on the concentrations of these acidic compounds (Goulding et al. 1998). Thus, it is likely more important in areas of high industrial activity or a high density of automobile traffic, but of lesser importance over rural areas. These ammonium compounds can then be removed by dry or wet deposition.

The vapor-phase reaction of ammonia with photochemically produced hydroxyl radicals is known to occur. The rate constants for this reaction have been determined to be $1.6x10^{-13}$ cm^3/molecule-sec, which translates to a calculated half-life of 100 days at a hydroxyl radical concentration of $5x10^5$ molecules/cm^3 (Graedel 1978). This process reportedly removes 10% of atmospheric ammonia (Crutzen 1983). Since ammonia is very soluble in water, rain washout is expected to be a dominant fate process. The half-life for ammonia in the atmosphere was estimated to be a few days (Brimblecombe and Dawson 1984; Crutzen 1983; Dawson 1977; Galbally and Roy 1983; Moller and Schieferdecker 1985). The reaction of atmospheric ammonia with acidic substances in the air results in the formation of ammonium aerosols that can subsequently be removed from the atmosphere by dry or wet deposition. In general, dry deposition processes predominate where there are high amounts of NH_3 emissions; where NH_3 emissions are lower, wet deposition of particulate NH_4^+ predominates (Asman et al. 1998).

6.3.2.2 Water

In surface water, groundwater, or sediment, ammonia can undergo sequential transformation by two processes in the nitrogen cycle, nitrification and denitrification, which would produce ionic nitrogen compounds, and from these, elemental nitrogen. The ionic nitrogen compounds formed from the aerobic process of nitrification, NO_2^- and NO_3, can leach through the sediment or be taken up by aquatic plants or other organisms. High concentrations of nitrate in groundwater can cause methemoglobinemia in infants when contaminated water is ingested (Messinga et al. 2003, Payne 1981). Elemental nitrogen formed from the anaerobic process of denitrification is lost by volatilization to the atmosphere.

In water, ammonia is in equilibrium with the ammonium ion, NH_4^+. The ammonia-ammonium ion equilibrium is highly dependent on the pH and, to a lesser extent, the temperature of the medium. In acidic waters and neutral waters, the equilibrium favors the ammonium ion.

6.3.2.3 Sediment and Soil

In soil, ammonia can serve as a nutrient source for plants, which can be taken up by plants and microorganisms and converted to organic-nitrogen compounds. Ammonia in soil can be rapidly transformed to nitrate by the microbial population through nitrification (Atlas and Bartha 1998; Payne 1981). The nitrate formed will either leach through the soil or be taken up by plants or other microorganisms. Very high localized concentrations of ammonia, such as those that might occur after a spill, or an excessive application, of ammonia-containing fertilizers can be toxic to plants, other organisms, or microbiota, which if inhibited or killed, will result in a decrease of the rates of any related nitrogen transformation processes. Under these conditions, other fate processes dictated by the physical and chemical properties of ammonia will dominate until the ammonia concentration returns to a background level. These physical and chemical processes include binding to soil particles (including organic carbon) or undergoing volatilization to the atmosphere.

6.3.2.4 Other Media

No data exist for the transformation or degradation of ammonia in other media, apart from biological tissues. These transformations are discussed in more detail in Chapter 3.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

In discussing the concentration of ammonia monitored in the environment, it is important to consider both ammonia and its conjugate acid, the ammonium ion. Independent determination of these compounds cannot always be achieved. In an analysis of the literature, it is difficult to separate aqueous ammonia concentration from aqueous ammonia-ammonium concentrations unless the investigators made a special effort to determine the amount of un-ionized ammonia. In this section of the document, ammonia will refer to the ammonia and ammonium concentration, and un-ionized ammonia will refer specifically to the ammonia concentration.

In the atmosphere, ammonia can exist in its gaseous state, be dissolved in rain, the water of fog, or clouds, or be found as ammonium in particulates and aerosols. These species can be analyzed separately. For this reason, atmospheric ammonia concentrations reported in this document will refer to the concentration of gaseous ammonia, and not to the concentrations of ammonium compounds.

6.4.1 Air

Ammonia has a worldwide atmospheric background concentration. Estimates of the average global ammonia concentration are approximately 0.6–3 ppb (Aneja et al. 1998; Crutzen 1983; Georgii and Gravenhorst 1977). Dawson and Farmer (1984) reported that the average concentration of ammonia in the southwestern United States is 0.9 ppb, which may be considered a representative background value because at the site of these measurements, the prevalent winds came from the Pacific Ocean and there were no known urban or agricultural ammonia sources nearby. Fangmeier et al. (1994) reported similar values in a review of effects of atmospheric ammonia on vegetation. Values measured at sea or at high altitude provided a background range of 0.06–1.0 ppb (n=9 reports). When atmospheric ammonia levels have been determined to be above background levels, the measurements can often be correlated with industrial, agricultural, or other activities that might occur in nearby areas (Fangmeier et al. 1994).

The concentrations of ammonia in the atmosphere vary across the United States, with concentrations being higher in the Midwest as compared to either the west or east coasts. Based on early data on the concentration of ammonia in rain, Lau and Charlson (1977) determined a trend for the atmospheric ammonia concentration across the United States. The estimation of atmospheric ammonia content increased progressively starting from the east coast to the mid-west and on to the western states. Upon reaching the Pacific coast, the atmospheric ammonia concentration decreases. It should be noted that the values obtained in this study (ppt levels over the eastern seaboard and pacific coasts, and low ppb levels in the midwest and western United States) tend to be lower than those determined by more recent experiments. For example, Aneja et al. (1998) measured concentrations of both NH_3 and NH_4^+ at Mount Mitchell (North Carolina) over 2 years; concentrations averaged 1–2 ppb. Fangmeier et al. (1994) provided atmospheric ammonia values derived from five studies conducted in the United States, with an average NH_3 concentration of 3.3 ppb. The general conclusion of Lau and Charlson (1977) however, appears valid, and is indicative of the trends found for the ammonia concentrations in the atmosphere. Atmospheric ammonia concentrations are expected to be highest near intense agricultural or livestock production areas because of ammonia emissions from fertilizer and animal excreta, respectively. Lower concentrations are generally expected in more industrialized areas because of diminished sources of agricultural emissions and the atmospheric reaction of ammonia with acidic compounds known to be produced in industrial emissions and automobile exhaust. Data summarized in Fangmeier et al. (1994) indicate that industrial regions may have significant ammonia concentrations, but these are orders of magnitude lower than concentrations in regions with some agricultural applications. Concentrations

determined near industrial sources in Germany (10.3–39.1 ppb) were in the same order of magnitude as concentrations near manure heaps (89 ppb), but were three orders of magnitude lower than emissions near pigpens ($4.7x10^4$ ppb).

Ground-level ammonia concentrations taken at urban Hampton and rural Langley, Virginia, ranged from 0.2 to 4.0 and from 1.5 to 4.0 ppb, respectively, in the fall of 1979 (Harward et al. 1982). Ammonia concentrations obtained in December of 1979 on Long Island, New York, ranged from approximately 80 to 200 nmol/m^3 (1.9–4.8 ppb) (Tanner 1982). The ground level ammonia concentrations in Claremont, Los Angeles, and Anaheim, California, were <25 ppb (Russell et al. 1988). In Riverside and Rubidoux, California, areas near dairy feedlots, the ground level ammonia concentrations were 37–132 ppb and approximately 10–100 ppb, respectively. Rural-area concentrations, however, in Massachusetts and New York were considerably lower (0.2–1.1 ppb) (Fangmeier et al. 1994).

The ambient concentrations of ammonia determined at Whiteface Mountain, New York, in 1982 ranged from approximately 0.3 to 5 ppb, with the hourly median and mean values both determined as 2.2 ppb (Kelly et al. 1984). Ammonia concentrations in rural Thurber, Nevada, ranged from approximately 0.5 to 2 ppb (Farmer and Dawson 1982). In the atmosphere over the world's oceans, ammonia concentrations ranged from approximately 0.28 to 5.6 ppb (Georgii and Gravenhorst 1977).

Several investigators have studied the seasonal variation of ammonia concentrations in the atmosphere. In Hampton, Virginia, the ground level ammonia concentrations during the spring and summer were 10 and 1 ppb, respectively (Levine et al. 1980). The difference in concentration may have been due to volatilization of ammonia resulting from springtime application of fertilizer in nearby agricultural areas. In Warren, Michigan, the average ammonia concentrations measured during the summer, fall, winter, and spring were 0.85, 0.37, 0.10, and 0.16 ppb, respectively. The difference in concentrations was attributed to fluctuations in emissions from livestock excreta, since natural ammonia emissions are much higher in the summer than in the winter (Cadle 1985; NRC 1979). Additionally, in colder weather, microbial activity would be expected to decrease, and thus, ammonia emissions from the decay of organic matter would also be expected to decrease. Ammonia emissions from animal excretions also fluctuate with the time of day (Beauchamp et al. 1982; Brunke et al. 1988).

The concentration of ammonia in the atmosphere decreases with altitude. Levine et al. (1980) found that an ammonia concentration of 10 ppb measured at ground level decreased to a concentration of 1.5–3 ppb at a height of 10 km. In a historical modeling study on the European production of ammonia, levels based

on ammonia release from livestock, fertilizer production and application, human and domestic animals, and sewage sludge resulted in average atmospheric ammonia concentrations ranging from 0.6 to 1.4 ppb for 1970 and from 0.7 to 5.6 ppb for 1980. The greatest increase occurred between 1950 and 1980, when synthetic fertilizer application and high nitrogen content feed grains were widely used (Asman and Drukker 1988). The ammonia concentration over a field during the application of gaseous ammonia fertilizer was as high as 300 ppb (Denmead et al. 1982). Over cattle feedlots, atmospheric ammonia concentrations have been measured at 520–2,160 ppb (Hutchinson et al. 1982).

6.4.2 Water

The concentration of ammonia in the Ochlocknee River at the head of Ochlocknee Bay, Florida, ranged from approximately 31 to 43 ppb, and concentrations of approximately 8.5 to 26 ppb were determined at the mouth of the bay (Seitzinger 1987). The concentration determined in the Ochlocknee River is consistent with levels reported for unpolluted tropical rivers (Meybeck 1982). Typical ammonia levels in the South Skunk River, Iowa, upstream from a municipal sewage-treatment facility were <1 ppm (Crumpton and Isenhart 1988). Downstream of the facility, ammonia levels peaked at approximately 16 mg/L (16 ppm), with levels of un-ionized ammonia ranging from <1.0 to 2.2 ppm. The levels of undissociated ammonia were directly related to pH fluctuations in the river. The authors did not discuss why the upstream concentration was so high. In the same study, it was noted that ammonium and un-ionized ammonia concentrations fluctuated in a diurnal pattern in the river, with peaks in ammonia (approximately 1 mg/L) occurring around noon, and low concentrations (0.5 mg/L) occurring usually after midnight (Crumpton and Isenhart 1988). The mean ammonia concentration in three Illinois rivers ranged from 0.28 mg/L (0.28 ppm) to 6.08 mg/L (6.08 ppm). The lower values were associated with agricultural sampling points and the higher values were associated with urban sampling points (Wilkin and Flemal 1980).

The ammonia concentration measured in Hamilton Harbour, Ontario, Canada was typically 0.1–3 mg/L (0.1–3 ppm) in the early 1980s. This body of water is used for water transportation (e.g., boat and barge traffic), as a source for industrial cooling water, and as a receptor for waste water disposal (Snodgrass and Ng 1985). Measurements made a few years later (1987–1988), in contrast, showed much lower concentrations. Measured concentrations, however, were still greater than the International Joint Commission objective of 20 ：g/L (20 ppb) for more than half the year, and concentrations often exceeded the chronic toxicity threshold of 300 ：g/L (300 ppb) (Barica 1990). This work reported that ammonia

loadings into Hamilton Harbor had decreased over the late 1970s and 1980s, and the measured concentrations may reflect that change.

Some representative data regarding the concentration of ammonia in groundwater indicate that natural concentrations are generally low, but that agricultural practices can, at times, lead to higher levels. Low levels of ammonia have been found in groundwater wells under cattle and poultry feed lots, and in shallow wells. Wells 3–6 m deep showed little variation in ammonia concentration over a 3-year period where varying amounts of chicken manure were spread over agricultural plots, except when excessive amounts (54–179 metric ton/ha) were applied (Liebhardt et al. 1979). Groundwater levels of ammonia were also determined in an area in Idaho that had previously been noted as having high nitrogenous compound concentrations in the water. In this study, ammonium concentrations varied from 2.5 ppb in a municipal drinking water well to 3.25 ppm in a deep, private well (Wicherski 2000). Shallow wells in North Carolina had typical ammonia concentrations of 0.1–1 ppm, which were independent of land use, plant type, and amount of fertilization (Gilliam et al. 1974). Water samples from wells on four schoolyards in Michigan that used septic tank sewage systems had ammonia concentrations ranging from 0 to 733 ppb (Rajagopal 1978). In the Netherlands, the ammonium concentration detected in sample cups buried 1.2 m in the ground near forests ranged from 0 to 2.3 ppm (Krajenbrink et al. 1988), but no ammonia was detected in deeper wells (12.6 meters) analyzed in this study. The high adsorptivity of ammonium to soil and the rapid conversion of ammonia to nitrate by microbial action are both consistent with the usual finding of very low ammonia concentrations in groundwater.

Ammonia was measured in rain and snow samples from three sites in northern Michigan in 1978–1979. Concentrations ranged from 23.8 to 3,500 ppb, with mean values for each site of 816, 572, and 632 ppb, respectively. Concentrations were generally greatest in the spring and fall and were lowest during the winter (Munger 1982). Ammonia concentrations in bulk precipitation obtained in the Netherlands had median values ranging from 1.33 ppm in ocean areas to 5.09 ppm in bodies of water near heavily agricultural areas (Schuurkes et al. 1988).

Ammonia concentrations in the influent to sewage-treatment plants, and thus the effluent from sewer systems, typically range from 10 to 20 ppm (Englande et al. 1978; Hauser 1984; U.S. Army Corps of Engineers 1980). Waste water-treatment plant effluent is one of the few types of point sources of ammonia emissions to surface water. In a study of several waste water-treatment plants, eight of nine plants exceeded the guideline ammonia concentration (0.5 mg/L), with measured median values at these sites ranging from 0.08 to 15 mg/L (0.08–15 ppm) (Englande et al. 1978).

No data were located in the available literature regarding ammonia concentrations in drinking water. This may be attributed to the rapid reaction between ammonia (and ammonium) and the chlorinating agents used in water treatment plants (Morris 1978).

6.4.3 Sediment and Soil

A 4-year study on ammonia levels in the soil (0–10 cm deep) of an open field (samples obtained in early May of each year) showed that ammonia concentrations ranged from 1 to 5 ppm (Beauchamp et al. 1982). The day after application of a slurry of liquid cow manure, the soil concentration ranged from 2 to 3,349 ppm. Five days after application, the concentration of ammonium ranged from 2 to 848 ppm. The greatest ammonia concentration was in the uppermost 4 cm of soil.

Ammonia was found at 137 of 1,647 hazardous waste sites on the NPL of highest priority sites for possible remedial action (HazDat 2004).

6.4.4 Other Environmental Media

The ammonia concentrations measured in the plumes of seven forest fires in the western United States ranged from 7 to 130 ppb; the median value of the 13 measurements was 37 ppb (Hegg et al. 1987, 1988). Fangmeier et al. (1994) reported a slightly higher value for smoke from a forest fire in Canada, 250 ppb. Ammonia has been found in the exhaust of automobile and diesel engines (Plerson and Brachaczek 1983). Ammonia has also been determined to be a component of tobacco and cigarette smoke (Sloan and Morie 1974).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The most probable routes by which the general population is exposed to ammonia are by the inhalation of ammonia that has volatilized from common household cleaning products and through dermal contact during the use of these products. Inhalation exposure to ammonia by some members of the rural population may occur for those who are near agricultural areas during the fertilizer-application period, those near animal feedlots or confinement areas, and those who apply anhydrous ammonia or ammonia-producing fertilizers to fields. There is also the possibility for exposure to ammonia via water and food

ingestion. If untreated surface water is ingested, the average uptake would be 0.36 mg/day (assuming an ammonia concentration in untreated water of 0.18 mg/L and a consumption of 2 L/day) (WHO 1986). Food ingestion could lead to an exposure to ammonia, primarily from the use of various ammonium salts as stabilizers; the estimated exposure from these food additives is 18 mg/day (WHO 1986).

In the National Occupational Hazard Survey (NOHS) of 1972–1974, it was statistically estimated that 2,524,678 workers are exposed to ammonia in the United States (RTECS 1988). According to the National Occupational Exposure Survey (NOES), in 1989, 681,780 workers (231,208 of whom were female) were estimated to be exposed to ammonia (NOES 1989). A correlation of data from the EPA Air Toxics Emission Inventory with industrial source codes (SIC codes) shows that volatile emissions of ammonia are associated with 212 different industrial classifications (EPA 1987b).

Workers in swine- and poultry-confinement buildings may be exposed to elevated levels of ammonia (Attwood et al. 1987; Crook et al. 1991; Donham and Popendorf 1985; Jones et al. 1984; Leonard et al. 1984; Liao and Bundy 1995). Average ammonia concentrations in the air of these buildings depend on numerous factors; representative values ranged from 0.28 to 42.2 ppm (280–42,200 ppb) (Attwood et al. 1987; Fangmeier et al. 1994), but in buildings with slow ventilation rates, concentrations exceeded 80 ppm (Liao and Bundy 1995). It should be noted that workers in these buildings may also be exposed to other materials in addition to ammonia, including particulate material (small dessicated manure particles), endotoxin, and others which may lead to combined exposures.

Ammonia levels in air at an ammonium phosphate fertilizer-production plant ranged from 3 to 75 ppm (3,000–75,000 ppb) (NIOSH 1987). In a Finnish plywood factory, short-term ammonia concentrations during the mixing of urea-formaldehyde glue were 50–70 ppm (50,000–70,000 ppb) (Kauppinen 1986). Ammonia concentrations at 42 facilities using a blue-line printing system were 1–40 ppm (1,000–40,000 ppb) (Tuskes et al. 1988). Workers at coal-gasification units may be exposed occupationally to ammonia (Jin et al. 1999; Van Hoesen et al. 1984). Workers at ammonia transportation and storage facilities can be exposed to ammonia during the transfer between facilities, from the venting of built-up pressure in tanks, and during leaks or spills.

Farmers can be exposed to ammonia when applying fertilizer. The ammonia concentration over a field during the application of gaseous anhydrous ammonia fertilizer was as high as 213 $\mu g/m^3$ (300 ppb) (Denmead et al. 1982). Workers at cattle production facilities (e.g., feedlots, farms) and those who work under conditions where volatilization from animal excreta would be enhanced may be occupationally

exposed to ammonia. Over cattle feedlots, atmospheric ammonia concentrations have been measured at 373–1,540 μg/m^3 (520–2,160 ppb) (Hutchinson et al. 1982). Exposure to ammonia can occur by inhalation in the liquid manure-storage facilities of swine-confinement buildings. Ambient air levels have been measured at up to 50 ppm (50,000 ppb) in these facilities (Donham et al. 1982).

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).

Three recent studies focused on the exposure of children to ammonia or the effects that exposure may have on children, all of which noted little effect on the children's health (Gomzi 1999; Gomzi and Saric 1997; Suh et al. 1992). One of the studies focused on the respiratory effects among people living near a fertilizer plant, another study investigated the effects of living in an urban vs. rural area, and a third study investigated the general effects of acid aerosols on children living in a semi-rural area. In general, these studies noted that exposure to low levels of ammonia had very little impact on the health of the children. The studies did find that other factors, such as parental smoking, had more profound effects on the children's respiratory health.

One study compared the effects of living near a fertilizer factory on the respiratory health of 8–9-year-old children (Gomzi and Saric 1997). The study found that the air quality near a fertilizer plant was within acceptable limits for most of the measurement period, with only a few fluctuations beyond acceptable limits. While these fluctuations correlated somewhat with health parameters measured on children living nearby, the rate of respiratory disease was more influenced by indoor air pollution sources than by

outdoor sources. No significant effect was observed due to exposure to ammonia at the concentrations seen in the study.

A second study of 223 children (8–10 years old) living in Croatia found that indoor air quality had a slightly greater effect on respiratory health in urban areas compared to those living in rural areas (Gomzi 1999). The differences, however, were not significant. The study found no influence of ammonia on the children's respiratory health, but did find that parental smoking had a significant negative impact on their respiratory health.

A third study evaluated SO_4^{2-} and H^+ exposure to 24 children (ages were not provided) living in Uniontown, Pennsylvania (Suh et al. 1992). This study did not focus on ammonia exposure *per se*, but on other airborne contaminant concentrations in aerosols found outdoors, indoors, and by personal monitors. It sought to determine how personal exposures to these aerosols correlated with indoor and outdoor concentrations. Ammonia concentrations were measured in order to assess their potential for neutralizing H^+ found in aerosols. Ammonia concentrations were found to be highest near the children (detected by the personal monitors), followed by indoor concentrations, and were minimal outdoors. It was proposed that a large proportion of the H^+ found in indoor aerosols are neutralized by NH_3, and would thus lower the children's exposure to acid aerosols. The authors noted that more research is needed to fully model the influence of factors, including NH_3, on indoor acid aerosol exposure.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in industries that commonly use ammonia, especially if there are no adequate safety and/or venting systems, may be at risk for potentially high exposure to ammonia. Examples of these might include farm workers who are employed in inadequately-ventilated, enclosed spaces with high concentrations of animals. Other examples include workers who process ammonia or transfer it from shipping containers to pipelines. The general population is at risk to high levels of exposure if cleaning products containing concentrated solutions of ammonia are used in small, enclosed, or unventilated rooms.

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 ammonia 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 ammonia.

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

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of ammonia have all been well documented, and there do not appear to be any data needs in this area.

Production, Import/Export, Use, Release, and Disposal. The large amounts of ammonia produced in nature and in household products indicate that the risk for human exposure to ammonia exists. Data regarding the commercial production, disposal, and use of ammonia are well understood. Data regarding the production of ammonia by natural organisms, and its global and regional concentrations are not as well understood, nor are the influences of different process strategies on livestock ammonia emissions. This information would be useful in determining the contribution of anthropogenic ammonia to the global budget of this compound, which would help in determining the human influence on the global cycle.

According to the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA), (§313), (Pub. L. 99-499, Title III, 9313), industries are required to submit release information to the EPA. The TRI contains release information for 2001. This database is be updated yearly and provides a more reliable estimate of industrial production and emission.

Environmental Fate. Since ammonia is a key intermediate in the nitrogen cycle, the environmental fate of ammonia should be interpreted in terms of its involvement in this cycle. Information available on the environmental fate of ammonia is sufficient to define the basic trends, and data are available regarding the direction of changes in these trends resulting from changes in the key variables. There are many subtle facets of the fate of ammonia in the environment that depend on nature and its cycles. Thus, accurately predicting the environmental fate of ammonia is not possible with our present knowledge.

An understanding of the environmental fate of ammonia is important when considering that human contribution to the global ammonia budget has grown over the years. A complete understanding of the environmental fate of ammonia will then allow an understanding of any changes that might occur from the role of ammonia in the nitrogen cycle. Since all living organisms depend on the nitrogen cycle, either directly or indirectly, this information would allow any decisions concerning ammonia to be made in an informed and prudent manner.

Bioavailability from Environmental Media. The bioavailability of ammonia from air and water has been examined rather extensively in animals. Bioavailability from soil has not been studied, although it is not a likely source of exposure.

Food Chain Bioaccumulation. Ammonia is a naturally-occurring compound and a key intermediate in the nitrogen cycle. Since it is continually recycled in the environment, bioaccumulation, as it is usually considered, does not occur. Thus, data on this process are not warranted.

Exposure Levels in Environmental Media. As an intermediate in the nitrogen cycle, ammonia is naturally present in environmental media. Measurements of ammonia in environmental media are sufficient to distinguish between background concentrations and elevated concentrations. Data regarding ammonia levels in soil samples, however, appear not to be as complete as the database for air and water.

Determining low level concentrations of atmospheric ammonia in the presence of ammonium salts is difficult. Recently, investigators have been establishing new methods for the analysis of ammonia in the presence of ammonium compounds (see Chapter 7, Analytical Methods). If highly accurate values for low levels of ammonia are necessary, then a re-evaluation of older literature values might be necessary.

Exposure Levels in Humans. Data regarding the exposure levels of ammonia are sufficient for understanding the sources and approximate magnitudes of human exposure. Quantitative monitoring data

for specific circumstances, occupations, or events, as reported in the current literature, might be considered to be lacking. Monitoring data for ammonia concentrations in the average household are generally adequate. Reports indicate that while background indoor concentrations of chemicals such as ammonia are sometimes higher inside than outside the home, the levels of exposure do not generally have effects on residents. This exposure, however, would be expected to be higher when ammonia-containing cleaning products are used, or when other ammonia-containing compounds are used in the household, and effects under these conditions would depend on the exposure concentration and duration.

Exposures of Children. Data regarding the exposure levels of ammonia to children were not extensive enough for evaluating the sources and approximate exposures to children. As was found with data in the section for Exposure Levels in Humans above, quantitative monitoring data might be considered lacking. A few recent studies indicate that exposures to, and effects of, ammonia on children are generally minimal, and do not influence the respiratory health of the children studied. However, more studies could be conducted to verify these findings.

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 ammonia were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry (Agency for Toxic Substances and Disease Registry 1999). The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this compound.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2003) database and Current Research Information System (CRIS) database (USDA 2003) provide additional information obtainable from a few ongoing studies that may fill some of the data needs identified in Section 6.8.1. These studies are summarized below and in Table 6-2. Most of the studies are investigating approaches that reduce exposures to ammonia, emissions of ammonia during agricultural practices, and novel systems to reduce those emissions.

Table 6-2. Ongoing Studies on Environmental Fate and the Potential for Human Exposure to Ammonia

Investigator	Affiliation	Research description	Sponsor
Bazemore RA; Chen TC	Mississippi State University	Evaluation of effectiveness of five substances (copper chlorophyllin complex, chitosan, activated carbon, kenaf, and paper mill sludge) in reducing ammonia emissions from animal waste compost.	Hatch
Harper LA; Sharpe RR	ARS, Athens, Georgia	Investigation of the generation and deposition of ammonia aerosols from swine waste, which is then compared to meteorological fluxes, with the objective being to reduce short-term and long-term ammonia losses that affect the local environment.	USDA in-house
Hristov AN	University of Idaho	This proposal seeks, through dietary means, better capture of ruminal ammonia-nitrogen into microbes and consequently into milk. This will increase the efficiency of utilization of feed N and reducing N excretions in the dairy cow.	NRI comp. grant
Walsh JL Jr.	Georgia Institute of Technology	The objective is to develop an integrated-optics (IO) sensor capable of measuring gaseous ammonia concentrations in the range of 100 ppb. This will be used to measure losses from agricultural croplands after application of nitrogen fertilizers.	U.S. DOE
Wilhelm LR et al.	University of Tennessee at Knoxville	Emission data and production information will be gathered from facilities country-wide for poultry and swine buildings. Evaluation of factors related to ammonia emissions will be conducted, and cost-effective approaches for reducing emissions considered and evaluated.	Hatch

Source: CRIS 2003; FEDRIP 2003

ARS = Agricultural Research Service; NRI = National Research Institute; USDA = U.S. Department of Agriculture; U.S. DOE = U.S. Department of Energy

Several studies are being conducted to lessen exposures to ammonia. Researchers at the University of Kentucky are investigating methods to reduce emissions of ammonia from poultry houses by improving manure handling. In a different approach, researchers at the University of Idaho are investigating changes in animal diet as a means to improve the abilities of livestock to more completely incorporate ruminal ammonia nitrogen into milk and protein. If successful, both will result in lower exposures to excreted ammonia. Furthermore, both approaches will lead to more knowledge regarding the efficient transformation of ammonia into useful products, either compostable manure or food products.

A considerable number of studies are being conducted to provide better determinations of atmospheric transport and deposition of ammonia, either on a local scale or a global scale, and for reducing ammonia effluents from animal waste. The U.S. Department of Agriculture (USDA) at Watkinsville and Athens, Georgia, in conjunction with the University of Tennessee at Knoxville, is investigating approaches to reduce ammonia emissions from poultry, dairy, and swine facilities, with the objective being to reduce short- and long-term ammonia losses that affect indoor and outdoor air quality. The USDA in Fayetteville, Arkansas is testing different approaches to reduce ammonia emissions from poultry, swine, and dairy facilities via evaluation of the efficacy of alum treatments. Other research efforts being conducted by the USDA include the evaluation of the best use and application practices of animal manures that contain ammonia to reduce emissions and favor nutrient transfer to crop soils. Mississippi State University researchers are evaluating the quality of poultry effluents and swine litter for use as manure-based fertilizers for crops, wherein the efficiency of manure nutrient (including ammonia) transfer to the crop soils is being evaluated. Research is also being conducted at Mississippi State University to evaluate the use of cellulosic materials (i.e., kenaf) to decrease ammonia and odor emissions from poultry waste. Kenaf has several attractive characteristics as a biosorbent for ammonia, and is therefore being evaluated for the removal of odors and ammonia from waste streams. In another study being conducted at Mississippi State University, five treatments (copper chlorophyllin, chitosan, activated carbon, kenaf, and paper mill sludge) are being compared for their effects on reducing emissions from poultry litter. The findings indicate that the materials have different efficiencies for reducing overall odor emissions, but no report has been provided about their specific effects on ammonia emissions.

7. ANALYTICAL METHODS

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

When ammonia is found in biological materials at physiological pH (7.2), most of it (99%) will be found as ammonium ion, due to its pK_a of 9.2. This is an important consideration for any subsequent analysis. The determination of ammonia (as dissolved NH_3 and ammonium ion) in blood, plasma, or serum is of value in detecting existing or impending hepatic coma and Reyes Syndrome (Meyerhoff and Robins 1980; Tietz 1970). The determination of ammonia in urine had historically been used as an indicator of the kidney's ability to produce ammonia; however, this procedure has been replaced by more modern and accurate tests for kidney function. Procedures for the determination of ammonia in biological samples are found in Table 7-1. Ammonia is also tested for in calculi (abnormal concretions in the body formed of mineral deposits, often found in the gall bladder, kidney, or bladder) (Tietz 1970); however, the test described therein is not quantitative and is not included in Table 7-1.

The amount of ammonia in collected blood, urine, saliva, or other biological fluid samples can be affected by several mechanisms that may lead to erroneous ammonia concentration determinations. These effects can be minimized by proper sample storage and handling. The ammonia content of freshly drawn blood rises rapidly on standing because of the deamination of labile amides such as glutamine (Henry 1964); at room temperature, the ammonia content can increase by a factor of two or three in several hours. Therefore, it is important to both keep the specimen cold (on ice) and perform the analysis as soon as possible. If the sample cannot be analyzed quickly, it may be frozen (-20 °C). The ammonia content of

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	24-Hour specimen, add HCl, refrigerate	Colorimetric (Berthelot reaction)	Not reported	Not reported	Tietz 1970
Urine	24-Hour specimen analyzed immediately, or stored up to 8 weeks at -20 °C	Indophenol reaction	Not reported	Not reported	Huizenga et al. 1994
Saliva	Freeze at -20 °C for up to 2 weeks, or store for 1 hour at 4 °C, or analyze immediately	Membrane based ammonia-selective electrode	Not reported	Not reported	Huizenga et al. 1994
Serum, plasma, whole blood	Freeze, then store at -15 °C for several days, or store on ice (4 °C) for 30–60 minutes, or analyze immediately	Colorimetric assay based on indophenol production	Not reported	Not reported	Huizenga et al. 1994
Serum, plasma, whole blood	Freeze, then store at -15 °C for several days, or store on ice (4 °C) for 30–60 minutes, or analyze immediately	Titration	Not reported	Not reported	Huizenga et al. 1994
Serum, plasma, whole blood	Freeze at -30 °C or store on ice, or analyze immediately	Membrane based ammonia-selective electrode	Not reported	-7.0–14% error, 102% average recovery	Meyerhoff and Robins 1980

iced (4 °C) blood samples remains constant for up to 60 minutes, whereas the ammonia content of frozen (-20 °C) blood samples remains constant for several days (Huizenga et al. 1994; Tietz 1970). For blood samples collected from a healthy person (and stored on ice), the ammonia content should be measured within 30–60 minutes of collection. For persons suspected of suffering from liver disease, however, the blood samples should be analyzed within 15 minutes (Huizenga et al. 1994). This more rapid assessment is necessary because some liver diseases result in high levels of γ-glutamyl transferase, an enzyme that hydrolyzes glutamine; the enzyme's activity will increase the concentration of ammonia in the sample to levels higher than was present at the time of collection (Huizenga et al. 1994). Other erroneously high measured ammonia levels can result from ammonia contamination of reagents or pick-up of ammonia from the atmosphere, including from technicians that have recently smoked a cigarette (Huizenga et al. 1994). The presence and activities of bacteria in samples can also cause changes in the concentrations of ammonia. The natural presence of bacteria present in some samples (e.g., saliva) or their presence in infected tissues (e.g., bladder infections) can lead to erroneously high ammonia concentrations, due to the presence of bacterial ureases that hydrolyze urea present in the biological samples. This reaction is the chief cause for the formation of ammonia in unacidified urine on standing (Henry 1964). Furthermore, contamination of samples by environmental bacteria following the collection of the sample may also lead to increases in ammonia concentrations. Therefore, use of sterile collection bottles for sample collection and storage is recommended if there is potential for storage of the sample prior to analysis (Huizenga et al. 1994).

In the determination of ammonia or ammonium ion in biological samples, ammonia is first liberated by distillation, aeration, ion-exchange chromatography, microdiffusion, or deproteinization (Huizenga et al. 1994). Deproteinization methods involve treatment of blood or plasma fluids with trichloroacetic acid (or perchloric acid or tungstate-sulfuric acid), followed by centrifugation. The protein-free supernatant can be assayed colorimetrically for ammonia. Traditionally, Kjeldahl distillation methods have been used to determine ammonia levels in biological tissue, but other methods (e.g., colorimetric or ion-specific electrodes) are also available. In the Kjeldahl distillation, ammonia is distilled and subsequently trapped in acid and analyzed titrametrically or colorimetrically. High values sometimes result because of the cleavage of protein amino groups and also the formation of ammonia by deamination reactions (Parris and Foglia 1983). Other techniques use the ammonia-selective electrode and enzymatic assays. Discrepancies have been reported between results using electrodes and those using more specific enzymatic procedures because the ammonia electrode responds to both ammonia and volatile amines (Parris and Foglia 1983). Chromatographic separation of ammonia and volatile amines after derivatization has also been used to obtain specificity (Huizenga et al. 1994; Parris 1984). Ammonia in

urine has been measured by Nesslerization, as well as by enzymatic assays and chromatographic approaches (Huizenga et al. 1994).

7.2 ENVIRONMENTAL SAMPLES

Water and waste water samples can be analyzed for ammonia by EPA Test Methods 1689 (EPA 2001a), 1690 (EPA 2001b), and 349.0 (EPA 1997). Analogous procedures (i.e., Method APHA 4500) have been approved and published jointly by the American Public Health Association, American Water Works Association, and Water Pollution Control Association. These methods are suitable for drinking, surface, and saline waters, and domestic and industrial effluent, and can be applied to biosolids. These and other methods for determining ammonia in environmental samples are listed in Table 7-2. Ammonia is reported as ammonia nitrogen. Two methods that are suitable for water employ colorimetric techniques, Nesslerization, and phenate methods. Nessler's reagent, an alkaline mixture of mercuric and potassium iodide, produces a yellow to brown color with ammonia, whereas the phenate reagent, alkaline phenol, and hypochlorite produce a blue color (EPA 2001a, 2001b; Greenberg et al. 1985). In the titrimetric method, the distillate is titrated with standard sulfuric acid with an appropriate indicator. The ammonia electrode employs a hydrophobic gas-permeable membrane to separate the sample solution from an internal ammonium chloride solution: ammonia diffusing through the membrane changes the pH of the internal solution and is sensed by a pH electrode. For determining NH_3-N concentrations above 5 mg/L, the titrimetric and ammonia-selective electrode methods are preferred. In contrast, gas chromatography/ mass spectrometry methods have been developed that permit NH_3 detection at concentrations near 20 μg/L for environmental waters (Mishra et al. 2001). Methods for determining ammonia in water and soil measure ammoniacal nitrogen, the sum of NH_3 and NH_4^+. In the determination of ammoniacal nitrogen in soil, exchangeable ammonium should be distinguished from nonexchangeable ammonium. The former is usually defined as that which can be extracted with KCl (or K_2SO_4) at room temperature (Bremner 1965). Nonexchangeable ammonium ion is defined as nitrogen held by clays and not displaced by 2M KCl (Bremner 1965). In the determination of nonexchangeable ammonium, organic forms of ammonia are first removed, the minerals containing the nonexchangeable ammonium are then decomposed with HF, and the ammonium ions released. In colorimetric procedures, turbidity and sample color may lead to interference. To eliminate interference, the pH of the sample may be raised and the ammonia distilled. Care should be taken to prevent losses in water samples due to volatilization and microbial transformation. To prevent such losses, samples should be acidified soon after collection and refrigerated. Care should also be taken during storage and treatment of soil samples to prevent ammonia

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Passive collection using 0.01 N H_2SO_4 in liquid sorbent badge	Method 6701, ion chromatography, conductivity detection	1 µg NH_3/sample	No bias between 6.9 and 48 ppm; +19% at 148 ppm	NIOSH 1987
Air	Air samples from stack emissions collected through an in-stack filter to remove particulates and ammonium salts, and then bubbled through 0.1 N H_2SO_4	EPA Method 30; ion chromato-graphy	1 µg NH_3/sample	98.5±1.3%; Bias of 0.996 ppm for a spiked sample of 6.43 ppm. Correction factor of 0.87 needs to be applied	Eaton et al. 1996
Air	0.8 µm prefilter may be used; ammonia trapped on sulfuric acid silica gel	NIOSH method 6015, Colorimetric determination of indophenol by visible light spectrophotometry	0.5 µg NH_3/sample	Not determined	NIOSH 1994
Air	0.8 µm prefilter may be used; ammonia trapped on sulfuric acid silica gel	NIOSH method 6016. Ion chromatography	2 µg NH_3/sample	102±3.8%	NIOSH 1996
Air	Chromatomembrane cells preextract and preconcentrate sample	Ion chromato-graphy with conductivity detection	6 µg NH_3/sample	Not reported	Erxleben et al. 2000
Air	Collection in H_2SO_4-coated activated carbon beads in sampling tube	Ion chromato-graphy	2 µg NH_3/sample	95–110% recovery	Bishop et al. 1986
Air	Known volume of air drawn through prefilter and H_2SO_4-treated silica gel	NIOSH S347, ammonia-specific electrode	Not reported	97.6% mean recovery	SRI 1988
Water	Sample mixed with borate buffer	Method 1689, ion selective probe	0.1 mg/L	Not reported	EPA 2001a

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Sample collected, preserved with H_2SO_4, and chilled to 4 °C. Samples should not be stored for >28 days	Method 1690, colorimetric determination of indophenol blue, following reaction of any ammonia with alkaline phenol and hypo-chlorite	0.2 mg/L	Not reported	EPA 2001b
Water	None	Method 350.1 colorimetric, automated phenate	0.1 mg/L	107 and 99% recoveries at 0.16 and 1.44 mg NH_3-N/L, respectively	EPA 1983
Estuarine and coastal water	Samples filtered through 0.45 µm membrane filter, refrigerated and analyzed within 3 hours	Method 349.0, automated colorimetric determination by reactions that form indophenol blue	0.3 µg/L	92.2–109.1% recovery, n=14	EPA 1997a
Water	Removal of residual chlorine with sodium thiosulfate, distillation	Method 350.2 Nessier reagent, colorimetric, titrimetric; or ammonia specific electrode	0.05 mg N/L for colorimetric and potentiometric; 1.0 mg N/L for titrametric	28.12 to -0.46R bias between 0.21 and 1.92 mg N/L	EPA 1983
Water	None	Method 350.3 ion selective electrode	0.03 mg N/L	96 and 91% recoveries at 0.19 and 0.13 mg N/L, respectively	EPA 1983
Soil, exchange-able ammonium	Extract soil with 2N KCl	Method 84-3, steam distillation with MgO, titration	Not reported	Not reported	Bremner 1965
Soil, non-exchangeable (fixed) ammonium	Pretreat soil with KOBr-KOH, shake with 5 N HF-1N HCl for 24 hours	Method 84-7, steam distillation with KOH, titration	Not reported	Not reported	Bremner 1965

loss or gain. It has been demonstrated that dry soil can rapidly adsorb trace amounts of ammonia from the atmosphere and that extensive amounts of ammonia can be lost during air drying (Bremner 1965). Additionally, in samples containing both ammonium and nitrite, losses during air drying may occur due to the reaction between these ions and the resulting formation and release of nitrogen gas (Bremner 1965).

The detection limit of analytical methods for determining ammonia in air depends on the amount of air collected in a liquid or solid adsorbent. Sampling is performed with passive samplers or by drawing a volume of air through the adsorbent using a pump. Particulate contaminants such as ammonium salts may be removed by a prefilter. For determination of ammonia in the ambient atmosphere, larger volumes of air must be sampled than those appropriate for determinations of ammonia in occupational settings (e.g., industrial, agricultural) where ammonia levels are higher. Improvements in methodologies have led to development of techniques that permit continuous monitoring of atmospheric ammonia down to 0.1 μg/m^3 (Pranitis and Meyerhoff 1987). Several passive monitoring systems report detection limits of 0.05–1.0 μg/m^3 and have collection rates ranging from 2.7 to 2,000 mL/minute (Kirchner et al. 1999). One method used for ambient atmospheric sampling employs a specially designed flow-through, ammonia-selective electrode with a sniffer tube, whereas the methods used for occupational settings often use passive collectors with media (usually acids impregnated onto filters) housed within protective cases. Ammonia concentrations on these passive collectors are then determined by a wide range of methods, including colorimetric assays (e.g., indophenol determination), the Berthelot reaction, or ion chromatography (Kirchner et al. 1999).

Ammonia may be present in air in both the vapor phase as ammonia gas and in the particulate phase as ammonium salts. While some analytical methods may distinguish between these phases, most standard methods do not. Methods have been developed that determine gaseous ammonia alone or gaseous and particulate forms of ammoniacal nitrogen separately. These methods use filter packs or sampling tubes coated with a selective adsorbent (denuder tube) to separate the phases (Dimmock and Marshall 1986; Knapp et al. 1986; Rapsomanikis et al. 1988). In these methods, gaseous ammonia is trapped by acids that act as adsorbents (e.g., citric acid, oxalic acid, phosphoric acid) on a coated filter or denuder tube (Kirchner et al. 1999). In filter methods, errors may arise due to ammonia interactions occurring on the filter and volatilization of retained ammonium salt (Dimmock and Marshall 1986; Rapsomanikis et al. 1988). There is evidence that ammonium nitrate in particulate matter is in equilibrium with ammonia. The presence of ammonium nitrate may lead to overestimation of the actual concentration of ammonia, but underestimation of the concentration of ammonium (Doyle et al. 1979). For additional review of the

methodologies for determining ammonia in water and air, see MacCarthy et al. (1987) and Fox (1987), respectively.

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 ammonia 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 ammonia.

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. No known unique biomarkers for exposure or effects exist for ammonia. Until one has been identified, methodology for the determination of biomarkers must be preceded by an experimental determination of a unique biomarker of human exposure or effect.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining ammoniacal nitrogen in environmental media are well developed and adequate. Standardized methods are available from EPA, NIOSH, and other sources. Analytical methods are also well developed for oxidation products of ammonia. Since there are multiple sources of these compounds in the environment, their analysis is not generally used to study the disappearance of ammonia.

7.3.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2003) database provides additional information obtainable from a few ongoing studies that may fill some of the data needs identified in Section 7.3.1. These studies are summarized below and in Table 7-3. By and large, most of the studies that were reported were related to the detection and measurement of atmospheric ammonia concentrations. Many of these focused on the development of novel sensor devices, which would provide better data for estimating ammonia emission and deposition rates. A company in Atlanta, Georgia is developing an optical ammonia sensor to measure agricultural emissions. This sensor is capable of detecting ammonia concentrations at the 100 ppb range and above. Similarly, the Georgia Institute of Technology is developing an optical sensor that will permit measurements of ammonia in the atmosphere at the 100 ppb range. Another company in Burlington, Massachusetts is developing a diode laser absorption remote sensor for measuring ammonia at trace concentrations, but no detection ranges have been specified. Another company in Massachusetts is developing a solid-state electrochemical sensor that is based on ionomer (i.e., an ion-containing polymer) membrane technology. This technology, however, is not intended for atmospheric ammonia sampling, but for instrument monitoring where ammonia gas may have negative impacts. This particular application seeks to produce these monitors for use in fuel cell systems, where free ammonia can negatively impact performance.

Table 7-3. Ongoing Studies on the Development of Analytical Approaches to the Study of Ammonia

Investigator	Affiliation	Research description	Sponsor
Attar AJ	Perfect View, Inc., Raleigh, North Carolina	Development of a low-cost ammonia detector (a small detector panel, about the size of a credit card, that changes color in response to ammonia in the atmosphere) for use in animal production facilities.	SBIR
Edwards J	Photonic Sensors, Atlanta, Georgia	Development of an optical ammonia sensor to measure agricultural emissions. This sensor is capable of detecting ammonia concentrations at the 100 ppb range.	Cooperative Agreement
Goldstein N	Spectral Sciences, Burlington, Massachusetts	Development of a diode laser absorption sensor for measurement of trace concentrations of ammonia, for potential applications in atmospheric chemistry and pollution monitoring.	U.S. DOE
Laconti AB	Giner, Inc., Waltham, Massachusetts	Development of a solid-state electrochemical sensor that is based on ionomer membrane technology for instrument monitoring where ammonia gas may have negative impacts.	SBIR
Ozanich RM	Northwest Instrument Systems, Richland, Washington	Development of an online system for analyzing ammonia (and other nitrogen containing chemicals) in water systems.	SBIR
Walsh JL Jr.	Georgia Institute of Technology, Atlanta, Georgia	Development of an optical ammonia sensor to measure agricultural emissions. This sensor is capable of detecting ammonia concentrations at the 100 ppb range, and would be useful for real-time monitoring of the injection of anhydrous ammonia fertilizer onto crops.	U.S. DOE

Source: FEDRIP 2002, 2003

SBIR = Small Business Innovative Research; U.S. DOE = U.S. Department of Energy

8. REGULATIONS AND ADVISORIES

International guidelines for ammonia were not located. National and state regulations and guidelines pertinent to human exposure to ammonia are summarized in Table 8-1.

ATSDR has derived an acute-duration inhalation MRL of 1.7 ppm for ammonia based on a minimal LOAEL of 50 ppm for eye, nose, and throat irritation in a study with volunteers (Verberk et al. 1977). No NOAEL was identified in that study. An uncertainty factor of 30 (3 for the use of a minimal LOAEL and 10 to protect sensitive individuals) was applied to the LOAEL.

ATSDR has derived a chronic-duration inhalation MRL of 0.1 ppm for ammonia based on a NOAEL of 9.2 ppm for sense of smell, prevalence of respiratory symptoms (cough, bronchitis, wheeze, dyspnea, etc.), eye and throat irritation, and pulmonary function parameters in workers exposed for approximately 12 years in a soda ash plant (Holness et al. 1989). No LOAEL was defined in that study. The NOAEL was duration-adjusted, and divided by an uncertainty factor of 10 to protect sensitive individuals. A modifying factor of 3 was added for the lack of reproductive and developmental studies. This MRL supersedes the previous chronic inhalation MRL of 0.3 ppm derived in the 2002 draft for public comment version of this profile.

EPA derived an inhalation reference concentration (RfC) of 1E-1 mg/m^3 (0.14 ppm) for ammonia based on a NOAEL of 6.4 mg/m^3 (9.2 ppm) defined in the Holness et al. (1989) study (IRIS 2004). EPA used an uncertainty factor of 30 (10 to protect sensitive individuals and 3 for data base deficiencies).

Ammonia has not undergone a complete evaluation under EPA's IRIS program for evidence of human carcinogenic potential.

Ammonium ion is regulated by the Clean Water Effluent Guidelines for the following industrial point sources: ferroalloy manufacturing; fertilizer manufacturing; glass manufacturing; inorganic chemicals; iron and steelmaking; landfills; nonferrous metals manufacturing; nonferrous metals forming and metal powder; paper and paperboard; petroleum refining; pharmaceutical manufacturing; pulp, meat products; and transportation equipment cleaning (EPA 2002j).

The FDA (1973) determined that concentrations of ammonia and ammonium compounds normally present in food do not suggest a health risk; ammonia and ammonium ions are recognized to be integral components of normal metabolic processes. However, some restrictions have been placed on levels of ammonium salts allowable in processed of foods. Maximum allowable levels in processed foods are as follows: 0.04–3.2% ammonium bicarbonate in baked goods, grain, snack, foods and reconstituted vegetables; 2.0% ammonium carbonate in baked goods, gelatins and puddings; 0.001% ammonium chloride in baked goods and 0.8% in condiments and relishes; 0.6–0.8% ammonium hydroxide in baked goods, cheeses, gelatins and puddings; 0.01% monobasic ammonium phosphate in baked goods; and 1.1% dibasic ammonium phosphate in baked goods, 0.003% in nonalcoholic beverages, and 0.012% for condiments and relishes.

Table 8-1. Regulations and Guidelines Applicable to Ammonia

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	
WHO	Drinking water quality guideline		WHO 2002
	Ammonia		
	Threshold odor concentration	1.5 mg/L	
	Threshold taste concentration	35 mg/L	
	Health-based guideline	None proposed	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		ACGIH 2001
	Ammonia	25 ppm	
	Ammonium chloride fume	10 mg/m^3	
	STEL (15-minute TWA)		ACGIH 2001
	Ammonia	35 ppm	
	Ammonia chloride fume	20 mg/m^3	
EPA	Accidental release prevention; toxic endpoint		EPA 2002b
	Ammonia (anhydrous)	0.14 mg/L	40CFR68, Appendix A
	Ammonia (>20% concentration)	0.14 mg/L	
	Regulated toxic substance for accidental release prevention under Section 112(r) of the Clean Air Act; threshold quantity		EPA 2002a
	Ammonia (anhydrous)	10,000 pounds	40CFR68.130, Table 1
	Ammonia (>20% concentration)	20,000 pounds	
	AEGL 1 (interim)	30 ppm	EPA 2004
NIOSH	REL (10-hour TWA)		NIOSH 2002b
	Ammonia	25 ppm	
	Ammonium chloride fume	10 mg/m^3	
	STEL (15-minute TWA)		NIOSH 2002b
	Ammonia	35 ppm	
	Ammonium chloride fume	20 mg/m^3	
	IDLH		NIOSH 2002b
	Ammonia	300 ppm	
	Ammonium chloride fume	No data	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2002d 29CFR1910.1000, Table Z-1
	Ammonia	50 ppm	

Table 8-1. Regulations and Guidelines Applicable to Ammonia

Agency	Description	Information	References
NATIONAL *(cont.)*			
OSHA	PEL (8-hour TWA) for construction industry		OSHA 2002c 29CFR1926.55, Appendix A
	Ammonia	50 ppm	
	PEL (8-hour TWA) for shipyard industry		OSHA 2002a 29CFR1915.1000
	Ammonia	50 ppm	
	Highly hazardous chemical, toxic, and reactive for general industry; threshold quantity[a]		OSHA 2002e 29CFR1910.119, Appendix A
	Ammonia	10,000 pounds	
	Ammonia solutions (>44% of ammonia by weight)	15,000 pounds	
	Highly hazardous chemical, toxic, and reactive for construction industry; threshold quantity[a]		OSHA 2002f 29CFR1926.64, Appendix A
	Ammonia	10,000 pounds	
	Ammonia solutions (>44% of ammonia by weight)	15,000 pounds	
	Occupational safety and health standards; storage and handling of anhydrous ammonia		OSHA 2002g 29CFR1910.111
	Occupations involved in agriculture that are particularly hazardous for the employment of children below the age of 16	Transporting, transferring, or applying anhydrous ammonia	OSHA 1998 29CFR570.71(a)(11)
	Safety and health regulations for construction; blasting and use of explosives; common blasting agent is a mixture of ammonium nitrate and carbonaceous combustibles		OSHA 2002b 29CFR1926.914(e)
b. Water			
EPA	Hazardous substance designated pursuant to Section 311(b)(2)(A) of the Clean Water Act		EPA 2002h 40CFR116.4, Table A
	Ammonia		
	Ammonium chloride		
	Ammonium fluoride		
	Ammonium hydroxide		
EPA	Reportable quantity of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2002i 40CFR117.3
	Ammonia	100 pounds	
	Ammonium chloride	5,000 pounds	
	Ammonium fluoride	100 pounds	
	Ammonium hydroxide	1,000 pounds	

Table 8-1. Regulations and Guidelines Applicable to Ammonia

Agency	Description	Information	References
NATIONAL *(cont.)*			
USC	Assurances of availability of adequate supplies of chemicals necessary for treatment of water	Ammonia	USC 2002a 42USC300j
c. Food			
EPA	Residues from ammonium chloride, ammonium hydroxide, and ammonium sulfate are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally inactive) ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest		EPA 2002e 40CFR180.1001(c)
	Ammonium nitrate is exempt from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only		EPA 2002e 40CFR180.1001(d)
	The fungicide ammonia is exempted from the requirement of a tolerance when used after harvest on the raw agricultural commodities grapefruit, lemons, oranges, and corn grain for feed use only		EPA 2002f 40CFR180.1003
FDA	Direct food substances affirmed as generally recognized as safe	Ammonium chloride	FDA 2001a 21CFR184.1138
	Direct food substances affirmed as generally recognized as safe	Ammonium hydroxide	FDA 2001b 21CFR184.1139
FDA	Direct food substances affirmed as generally recognized as safe	Ammonium sulfate	FDA 2001c 21CFR184.1143
	Drug products containing certain active ingredients offered over-the-counter	Ammonium chloride	FDA 2001d 21CFR310.545(a)
	Expectorant drug product	Ammonia solution	
	Fever blister and cold sore treatment drug product	Ammonia solution and Ammonium hydroxide	
	Insect bite and sting drug products	Ammonium hydroxide	
	Food additives permitted in feed and drinking water of animals	Anhydrous ammonia	FDA 2001e 21CFR573.180
	Substance generally recognized as safe when used in accordance with good manufacturing or feeding practices	Ammonium hydroxide	FDA 2001f 21CFR582.1139

Table 8-1. Regulations and Guidelines Applicable to Ammonia

Agency	Description	Information	References
NATIONAL *(cont.)*			
	Substance generally recognized as safe when used in accordance with good manufacturing or feeding practices	Ammonium sulfate	FDA 2001g 21CFR582.1143
d. Other			
CPSC	Federal Caustic Poison Act		CPSC 2001
	Ammonia water and any preparation containing free or chemically uncombined ammonia, including ammonium hydroxide and “hartshorn”, in a concentration of 5% or more		16CFR1500.129(1)
EPA	Ammonia		IRIS 2004
	Carcinogenicity classification	No data	
	RfC	$1x10^{-1}$ mg/m^3	
	RfD	No data	
	CERCLA hazardous substance designated pursuant to Section 311(b)(4) of the Clean Water Act		EPA 2002d
	Reportable quantity		40CFR302.4(a)
	Ammonia	100 pounds	
	Ammonium chloride	5,000 pounds	
	Ammonium fluoride	100 pounds	
	Ammonium hydroxide	1,000 pounds	
EPA	Extremely hazardous substance		EPA 2002c
	Ammonia		40CFR355,
	Reportable quantity	100 pounds	Appendix A
	Threshold planning quantity	500 pounds	
	Toxic chemical release reporting; Community right-to-know; effective date for reporting		EPA 2002g
	Ammonia[b]	01/01/87	40CFR372.65(a)
	Ammonium nitrate (solution)	01/01/87[c]	
USC	Imposition of Superfund tax on any taxable chemical sold by the manufacturer, producer, or importer		USC 2002d
	Ammonia	$2.64 per ton	26USC4661
	Refund or credit of Superfund tax paid when ammonia is used as a fertilizer		USC 2002b 26USC4662
	Superfund taxable substance	Ammonium nitrate	USC 2002c 26USC4672
STATE			
Regulations and Guidelines:			
a. Air		No data	

Table 8-1. Regulations and Guidelines Applicable to Ammonia

Agency	Description	Information	References
STATE *(cont.)*			
b. Water		No data	
c. Food		No data	
d. Other		No data	
Florida	Toxic substance		BLR 2002
	Ammonia		
	Ammonium chloride		
	Ammonium fluoride		
	Ammonium nitrate		
	Ammonium sulfate		
Massachusetts	Hazardous substance		BLR 2002
	Ammonia		
	Ammonium chloride		
	Ammonium fluoride		
	Ammonium hydroxide		
	Ammonium nitrate		
	Ammonium sulfate		
Minnesota	Hazardous substance		BLR 2002
	Ammonia		
	Ammonium chloride, fume		
New Jersey	Hazardous substance		BLR 2002
	Ammonia		
New York	Hazardous substance		BLR 2002
	Ammonia		
	Ammonium chloride		
	Ammonium fluoride		
	Ammonium hydroxide		
Pennsylvania	Hazardous substance		BLR 2002
	Ammonia		
	Ammonium chloride		
	Ammonium fluoride		
	Ammonium hydroxide		

[a]Potential for a catastrophic event at or above the threshold quantity.
[b]Ammonia: includes anhydrous ammonia, aqueous ammonia from water, dissociable ammonium salts, and other sources; 10% of total aqueous ammonia is reportable under this listing.
[c]Ammonium nitrate (solution) is removed from this listing; the removal is effective 07/02/95, for the 1995 reporting year.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline value: BLR = Business & Legal Reports, Inc. CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; CPSC = Consumer Protection Safety Commission; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; IRIS = Integrated Risk Information System; NIOSH = National Institute of Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; ppm = parts per million; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

9. REFERENCES

ACGIH. 1988. Threshold limit values and biological exposure indices for 1988-1989. Cincinnati, OH. American Conference of Governmental Industrial Hygienists.

ACGIH. 1991. Ammonium chloride fume. Documentation of the threshold limit values: For chemical substances in the work environment. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

*ACGIH. 2001. Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

*Adamowicz RF. 1979. A model for the reversible washout of sulfur dioxide, ammonia and carbon dioxide from a polluted atmosphere and the production of sulfates in raindrops. Atmos Environ 13:105-121.

*Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. Environ Health Perspect Suppl 103(7):103-112.

Aelion CM, Shaw JN, Wahl M. 1997. Impact of suburbanization on ground water quality and denitrification in coastal aquifer sediments. J Exp Mar Biol Ecol 213(1):31-51.

*Agency for Toxic Substances and Disease Registry. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Fed Reg 54(174):37618-37634.

*Agency for Toxic Substances and Disease Registry. 1999. ATSDR National Exposure Registry (NER). http://www.atsdr.cdc.gov/faq/faqner.html. May 3, 2002.

Agte V, Chiplonkar S, Joshi N, et al. 1994. Apparent absorption of copper and zinc from composite vegetarian diets in young Indian men. Ann Nutr Metab 38(1):13-19.

Ahmad I, Ali S, Jan MR. 2000. Physico-chemical analysis of fertilizer industry effluent and its effects on crop plants. Pak J Sci Ind Res 43(2):83-89.

Albrecht J. 1998. Roles of neuroactive amino acids in ammonia neurotoxicity. J Neurosci Res 51(2):133-138.

Ali BA, Ahmed HO, Ballal SG, et al. 2001. Pulmonary function of workers exposed to ammonia: A study in the Eastern Province of Saudi Arabia. Int J Occup Environ Health 7(1):19-22.

Allen AG, Harrison RM, Erisman J-W. 1989. Field measurements of the dissociation of ammonium nitrate and ammonium chloride aerosols. Atmos Environ 23(7):1591-1599.

---

* Cited in text

9. REFERENCES

Allen WM, Sansom BF, Trower CJ. 1993. Bovine deaths associated with ammoniated straw. Vet Rec 132(16):419.

*Altman PL, Dittmer DS. 1974. Biological handbooks: Biology data book. Vol. III. 2nd ed. Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008, 2041.

Ambrose AM. 1943. Studies on the physiological effects of sulfamic acid and ammonium sulfamate. J Ind Hyg Toxicol 25(1):26-28.

*Amoore JE, Hautala E. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 3(6):272-290.

*Amshel CE, Fealk MH, Phillips BJ, et al. 2000. Anhydrous ammonia burns case report and review of the literature. Burns 26(5):493-497.

*Andersen ME, Krishnan K. 1994. Relating in vitro to in vivo exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, replacement. New York: Marcel Dekker, Inc., 9-25.

*Andersen ME, Clewell HJ III, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87:185-205.

Andersson BO. 1991. Lithuanian ammonia accident, March 20th 1989. Inst Chem Eng Symp Ser 124:15-17.

*Aneja VP, Murthy AB, Battye W, et al. 1998. Analysis of ammonia and aerosol concentrations and deposition near the free troposphere at Mt. Mitchell, NC, USA. Atmos Environ 32(3):353-358.

Anghileri LJ. 1975. Tumor growth inhibition by ammonium chloride-induced acidosis. Int J Clin Pharmacol 12:320-326.

*Ankley GT, Katko A, Arthur JW. 1990. Identification of ammonia as an important sediment-associated toxicant in the lower Fox River and Green Bay, Wisconsin. Environ Toxicol Chem 9:313-322.

Anonymous. 2003. Final report on the safety assessment of ammonium, potassium, and sodium persulfate. Int J Toxicol 20(3):7-21.

*Appelman LM, ten Berg WF, Reuzel PGJ. 1982. Acute inhalation toxicity of ammonia in rats with variable exposure periods. Am Ind Hyg Assoc J 43(9):662-665.

*ApSimon HM, Kruse M, Bell JNB. 1987. Ammonia emissions and their role in acid deposition. Atmos Environ 21:1939-1946.

*Arwood R, Hammond J, Ward GG. 1985. Ammonia inhalation. J Trauma 25 (5):444-447.

*Asman WAH, Drukker B. 1988. Modelled historical concentrations and depositions of ammonia and ammonium in Europe. Atmos Environ 22:725-736.

*Asman WAH, Janssen AJ. 1987. A long-range transport model for ammonia and ammonium for Europe. Atmos Environ 21:2099-2119.

9. REFERENCES

*Asman WAH, Sutton MA, Schjorring JK. 1998. Ammonia: Emission, atmospheric transport and deposition. New Phytol 139(1):27-48.

*Atlas RM, Bartha R. 1998. Biochemical cycling: nitrogen, sulfur, phosphorus, iron, and other elements. In: Fogel L, Wong G, eds. Microbial ecology. Fundamentals and applications. Menlo Park, CA: Benjamin/Cummings Science Publishing, 414-425.

*Attwood P, Brouwer R, Ruigewaard P, et al. 1987. A study of the relationship between airborne contaminants and environmental factors in Dutch confinement buildings. Am Ind Hyg Assoc J 48(8):745-751.

*Auerbach C, Robson JM. 1947. XXXIII-Test of chemical substances for mutagenic action. Proc R Soc Edinb (Nat Environ) 62:284-291.

*Ayers GP, Gillett RW, Caeser ER. 1985. Solubility of ammonia in water in the presence of atmospheric CO_2. Tellus 37B:35-40.

*Bachmann C. 2002. Mechanisms of hyperammonemia. Clin Chem Lab Med 40(7):653-662.

Bai G, Rama Rao KV, Murthy ChRK, et al. 2001. Ammonia induces the mitochondrial permeability transition in primary cultures of rat astrocytes. J Neurosci Res 66(5):981-991.

*Ballal SG, Ali BA, Albar AA, et al. 1998. Bronchial asthma in two chemical fertilizer producing factories in eastern Saudi Arabia. Int J Tuberc Lung Dis 2(4):330-335.

Baraldi M, Pinelli G, Ricci P, et al. 1984. Toxins in hepatic encephalopathy: The role of synergistic effect of ammonia, mercaptans and short chain fatty acids. Arch Toxicol Suppl 7:103-105.

Barbieri P, Adami G, Predonzani S, et al. 1999. Survey of environmental complex systems: pattern recognition of physicochemical data describing coastal water quality in the Gulf of Trieste. J Environ Monit 3(2):210-216.

*Barica J. 1990. Ammonia and nitrite contamination of Hamilton Harbour, Lake Ontario. Water Pollut Res J Can 25(3):359-386.

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

*Barrow CS, Steinhagen WH. 1980. NH_3 concentrations in the expired air of the rat: Importance to inhalation toxicology. Toxicol Appl Pharmacol 53:116-121.

Barrow CS, Alarie Y, Stock M. 1978. Sensory irritation and incapacitation evoked by thermal decomposition products of polymers and comparisons with known sensory irritants. Arch Environ Health 33(2):79-88.

Barry DAJ, Goorahoo D, Goss MJ. 1993. Estimation of nitrate concentrations in groundwater using a whole farm nitrogen budget. J Environ Qual 22(4):767-775.

Barshaw ML, Wachtel RC, Cohen L, et al. 1986. Neurological outcome in premature infants with transient asymptomatic hyperammonemia. J Pediatr 108(2):271-275.

9. REFERENCES

*Barzel US. 1975. The effect of chronic ammonium chloride ingestion on parathyroid hormone function. Nephron 14:339-346.

*Barzel US, Jowsey J. 1969. The effects of chronic acid and alkali administration on bone turnover in adult rat. Clin Sci 36:517-524.

Basile AS. 2002. Direct and indirect enhancement of GABAergic neurotransmission by ammonia: implications for the pathogenesis of hyperammonemic syndromes. Neurochem Int 41:115-122.

*Bauer CF, Andren AW. 1985. Emissions of vapor-phase fluorine and ammonia from the Columbia coal-fired power plant. Environ Sci Technol 19:1099-1103.

Baum MM, Kiyomiya ES, Kumar S, et al. 2001. Multicomponent remote sensing of vehicle exhaust by dispersive absorption spectroscopy. 2. Direct on road ammonia measurements. Environ Sci Technol 35(18):3735-3741.

*Beare JD, Wilson RS, Marsh RJ. 1988. Ammonia burns of the eye: Old weapon in new hands. Br Med J 296:590.

*Beauchamp EG, Kidd GE, Thurtell G. 1978. Ammonia volatization from sewage sludge applied in the field. J Environ Qual 7:141-146.

*Beauchamp EG, Kidd GE, Thurtell G. 1982. Ammonia volatization from liquid dairy cattle manure in the field. Can J Soil Sci 62:11-19.

Benjamin AM, Okamoto K, Quastel JH. 1978. Effects of ammonium ions on spontaneous action potentials and on contents of sodium, potassium, ammonium and chloride ions in brain *in vitro*. J Neurochem 30:131-143.

*Benyajati S, Goldstein L. 1975. Renal glutaminase adaptation and ammonia excretion in infant rats. Am J Physiol 228:693-698.

Berenzen N, Schulz R, Liess M. 2001. Effects of chronic ammonium and nitrite contamination on the macroinvertebrate community in running water microcosms. Water Res 35(14):3478-3482.

*Berger GS. 1994. Epidemiology of endometriosis. In: Berger GS, ed. Endometriosis: Advanced management and surgical techniques. New York, NY: Springer-Verlag.

Berger S, Bermes EW, Blanke RV, et al. Ammonia. 1970. In: Tietz NW, ed. Fundamentals of clinical chemistry. Philadelphia, PA: W.B. Saunders Company, 665-731.

*Betterton EA. 1992. Henry's law constants of soluble and moderately soluble organic gases: effects on aqueous phase chemistry. In: Nriagu JO, ed. Gaseous pollutants: Characterization and cycling. Tuscon, AZ: John Wiley & Sons, Inc., 1-50.

*Beyrouty CA, Sommers LE, Nelson DW. 1988. Ammonia volatization from surface-applied urea as affected by several phosphoroamide compounds. Soil Sci Soc Am J 52:1173-1178.

Bilski J, Jaworek J, Cieszkowski M, et al. 1996. Exocrine pancreatic response to ammonia in vivo and in vitro. Digestion 57(4):219.

9. REFERENCES

*Bishop RW, Belkin F, Gaffney R. 1986. Evaluation of a new ammonia sampling and analytical procedure. Am Ind Hyg Assoc J 47:135-137.

Blade MC, Arola L, Alemany M. 1988. Rapid detoxification of infused ammonium by the anesthetized rat. Biochem Int 16(5):859-867.

*Blei AT, Olafsson S, Therrien G, et al. 1994. Ammonia-induced brain edema and intracranial hypertension in rats after portacaval anastomosis. Hepatology 19(6):1437-1444.

Blowey R, Packington A. 1994. Polioencephalomalacia associated with ingestion of ammonium sulphate. Vet Rec 134(24):636.

*Bodansky A, Jaffe HL, Chandler JP. 1932. Serum phosphatase changes in calcium deficiency and in ammonium chloride osteoporosis. Proc Soc Exp Biol Med 29:871-873.

*Bodega G, Suárez I, Boyano MC, et al. 1993. High ammonia diet: Its effect on the glial fibrillary acidic protein (GFAP). Neurochem Res 18(9):971-975.

*Bodega G, Suárez I, Rubio M, et al. 1991. Heterogeneous astroglial response in the rat spinal cord to long-term portacaval shunt. An immunohistochemical study. Glia 4:400-407.

*Bouwman AF, Lee DS, Asman WAH, et al. 1997. A global high-resolution emission inventory for ammonia. Global Biogeochem Cycles 11(4):561-587.

*Bouwmeester RJ, Vlek PLG. 1981. Rate control of ammonia volatization from rice paddies. Atmos Environ 15:131-140.

*Boyano-Adanez MC, Bodega G, Barrios V, et al. 1996. Response of rat cerebral somatostatinergic system to a high ammonia diet. Neurochem Res 29(5):469-476.

*Boyd EM, Seymour KGW. 1946. Ethylenediamine dihydrochloride or chlor-ethamine. II. Untoward and toxic reactions. Exp Med Surg 223-227.

*Boyd EM, MacLachlan ML, Perry WF. 1944. Experimental ammonia gas poisoning in rabbits and cats. J Ind Hyg Toxicol 26:29-34.

Braissant O, Henry H, Villard A, et al. 2002. Ammonium-induced impairment of axonal growth is prevented through glial creatine. J Neurosci 22(22):9810-9820.

*Bremner JM. 1965. Inorganic forms of nitrogen. In: Black CA, Evans DD, Ensminger LE, et al., eds. Agronomy. Methods of soil analysis. Part 2. Chemical and microbiological properties. Madison, WI: American Society of Agronomy, Inc., 1179-1237.

*Brimblecombe P, Dawson GA. 1984. Wet removal of highly soluble gases. J Atmos Chem 2:95-107.

*Brinson SEJR, Cabrera ML, Tyson SC. 1994. Ammonia volatilization from surface-applied, fresh and composted poultry litter. Plant Soil 167(2):213-218.

*BLR. 2002. Book of chemical lists on CD-Rom. Old Saybrook, CT: Business & Legal Reports, Inc.

9. REFERENCES

*Broderson JR, Lindsey JR, Crawford JE. 1976. The role of environmental ammonia in respiratory mycoplasmosis of rats. Am J Pathol 85:115-130.

Brooks KJ, Kauppinen RA, Williams SR, et al. 1989. Ammonia causes a drop in intracellular pH in metabolizing cortical brain slices: A phosphorus-31 and proton NMR study. Neuroscience 33(1):185-192.

*Brown RH, Duda GD, Korkes S, et al. 1957. A colorimetric micromethod for determination of ammonia; the ammonia content of rat tissues and human plasma. Arch Biochem Biophys 66:301-309.

*Brunke R, Alvo P, Schuepp P, et al. 1988. Effect of meteorological parameters on ammonia loss from manure in the field. J Environ Qual 17:431-436.

*Brunner H, Thaler H, eds. 1981. Hepatology: A festschrift for Hans Popper. New York, NY: Raven Press, 212.

*Budavari S, O'Neil MJ, Smith A, et al., eds. 1996. The Merck index, 12th ed. Whitehouse Station, NJ: Merck & Co. Inc., 87.

*Buff R, Koller EA. 1974. Studies underlying the reflex hyperpnoea induced by inhalation of chemical irritants. Respir Physiol 21:371-383.

Bugge M, Bengtsson F, Nobin A, et al. 1988. Serotonin metabolism in the rat brain following ammonia administration. In: Soeters PB, Wilson JHP, Meijer AJ, et al., eds. Advances in ammonia metabolism and hepatic encephalopathy. New York, NY: Excerpta Medica.

Bugge M, Bengtsson F, Nobin A, et al. 1989. The effect of ammonia infusion on brain monoamine metabolism in portacaval-shunted rats. Res Exp Med 189(2):101-111.

*Buijsman E, Maas HFM, Asman WAH. 1987. Anthropogenic NH_3 emissions in Europe. Atmos Environ 21(5):1009-1022.

Burkhard LP, Jenson JJ. 1993. Identification of ammonia, chlorine, and diazinon as toxicants in a municipal effluent. Arch Environ Contam Toxicol 25:506-515.

Burkitt DP. 1978. Workshop V - fiber and cancer. Summary and recommendations. Am J Clin Nutr 31:S213-S215.

*Burns TR, Greenberg SD, Mace ML, et al. 1985. Ultrastructure of acute ammonia toxicity in the human lung. Am J Forensic Med Pathol 6:204-210.

*Butterworth RF. 2002. Pathophysiology of hepatic encephalopathy: A new look at ammonia. Metab Brain Dis 17(4):221-227.

Bytnerowicz A, Fenn ME. 1996. Nitrogen deposition in California forests: A review. Environ Pollut 92(2):127-146.

*C & E News. 1987. Ammonia. Chem Eng News. March 2, 1987.

*Cadle SH. 1985. Seasonal variations in nitric acid, nitrate, strong aerosol acidity, and ammonia in an urban area. Atmos Environ 19(1):181-188.

Campbell CL, Dawes RK, Deolalkar S, et al. 1958. Effect of certain chemicals in water on the flavor of brewed coffee. Food Res 23:575-579.

Campbell SC. 1988. Severe ventilatory depression reversed with aromatic ammonia inhalation. N Engl J Med 319(8):1550.

*Caplin M. 1941. Ammonia-gas poisoning: Forty-seven cases in a London shelter. Lancet 241:95-96.

*Capuco AV. 1977. Ammonia: A modulator of 3T3 cell growth. Diss Abstr Int B 38(9):4085.

*Castell DO, Moore EW. 1971. Ammonia absorption from the human colon. Gastroenterology 60:33-42.

Chan H, Pannunzio M, Hazell AS, et al. 2001. Exposure to ammonia results in decreased glutamate transporter activity in cultured cerebellar granule cells. J Neurochem 78(Suppl 1):40.

Chapin RE, Gulati DK. 1997. Reproductive toxicology. Pesticed/fertilizer mix II (California). Environ Health Perspect Suppl 105(1):373-374.

Chou SF, Jacobs LW, Penner D. 1978. Absence of plant uptake and translocation of polybrominated biphenyls (PBBs). Environ Health Perspect 23:9-12.

*Choudat D, Goehen M, Korobaeff M, et al. 1994. Respiratory symptoms and bronchial reactivity among pig and dairy farmers. Scand J Work Environ Health 20(1):48-54.

Chourasia HK. 2001. Efficacy of ammonia in detoxification of fumonisin contaminated corn. Indian J Exp Biol 39(5):493-495.

*Christesen HB. 1995. Prediction of complications following caustic ingestion in adults. Clin Otolaryngol 20(3):272-278.

*Clark EC, Nath KA, Hostetter MK, et al. 1990. Role of ammonia in tubulointerstitial injury. Miner Electrolyte Metab 16(5):315-321.

*Clemmesen JO, Larsen FS, Kondrup J, et al. 1999. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology 29(3):648-653.

*Clewell HJ III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

*Clinton SK, Bostwick DG, Olson LM, et al. 1988. Effects of ammonium acetate and sodium cholate on N-methyl-N'-nitro-N-nitrosoguanidine-induced colon carcinogenesis of rats. Cancer Res 48:3035-3039.

*Close LG, Catlin FI, Cohn AM. 1980. Acute and chronic effects of ammonia burns of the respiratory tract. Arch Otolaryngol 106:151-158.

CLPSD. 1987. Contract Laboratory Program (CLP) Statistical Database. Alexandria, VA: Viar and Company, Management Services Division, April 1987.

CMR. 1988. Ammonia. Chemical Market Reporter. October 3, 1998. 51-52.

*CMR. 1999. Chemical profile ammonia. Chemical Market Reporter. November 29, 1999.

*Colborn T, Clement C, eds. 1992. Chemically-induced alterations in sexual and functional development: The wildlife human connection. Princeton, NJ: Princeton Scientific Publishing.

*Cole TJ, Cotes JE, Johnson GR, et al. 1977. Ventilation, cardiac frequency and pattern of breathing during exercise in men exposed to *o*-chlorobenzylidene malonitrile (CS) and ammonia gas in low concentrations. Q J Exp Physiol Cogn Med Sci. 63:341-351.

*Conn HO. 1972. Studies of the source and significance of blood ammonia IV. Early ammonia peaks after ingestion of ammonia salts. Yale J Biol Med 45:543-549.

*Coon RA, Jones RA, Jenkins LJ Jr, et al. 1970. Animal inhalation studies on ammonia, ethylene, glycol, formaldehyde, dimethylamine and ethanol. Toxicol Appl Pharmacol 16:646-655.

Córdoba J, Crespin J, Gottstein J, et al. 1999. Mild hypothermia modifies ammonia-induced brain edema in rats after portacaval anastomosis. Gastroenterology 116(3):686-693.

*Córdoba J, Gottstein J, Blei AT. 1998. Chronic hyponatremia exacerbates ammonia-induced brain edema in rats after portacaval anastomosis. J Hepatol 29(4):589-594.

*Cormier Y, Israel-Assayag E, Racine G, et al. 2000. Farming practices and the respiratory health risks of swine confinement buildings. Eur Resp J 15(3):560-565.

*Corsi RL, Torres VM, Fredenberg S, et al. 2000. A screening assessment of non-point source ammonia emissions in Texas. Proceedings of the Air & Waste Management Association's, 93rd Annual Meeting & Exhibition: Salt Lake City, Utah, June 18-22, 2000. Pittsburgh, PA: Air and Waste Management Association, 4279-4292.

*Coude FX, Grimber G. 1984. Inhibition of urea synthesis by pent-4-enoic acid: Potentiation by ammonia. Biochem Biophys Res Commun 118(1):47-52.

*Couturier Y, Barbotin M, Bobin P, et al. 1971. [Apropos of three cases of toxic lung caused by vapors of ammonia and hydrogen sulfide.] Bull Soc Med Afr Noire Lang Fr 16:250-252. (French)

*CPSC. 2001. Hazardous substances and articles; administration and enforcement regulations. Substances named in the Federal Caustic Poison Act. Consumer Product Safety Committee. Code of Federal Regulations. 16 CFR 1500.129(1). http://frwebgate.access.gpo.gov/cgi. May 02, 2002.

*CRIS. 2003. Ammonia. Current Research Information Systems. http://cris.csrees.usda.gov/. July 01, 2004.

*Crook B, Robertson JF, Travers Glass SA, et al. 1991. Airborne dust, ammonia, microorganisms, and antigens in pig confinement houses and the respiratory health of exposed farm workers. Am Ind Hyg Assoc J 52(7):271-279.

*Crumpton WG, Isenhard TM. 1988. Diurnal patterns of ammonium and un-ionized ammonia in streams receiving secondary treatment effluent. Bull Environ Contam Toxicol 40(4):539-544.

9. REFERENCES

*Crutzen PJ. 1983. Atmospheric interactions--homogeneous gas reactions of C, N, and S containing compounds. In: Bolin B, Cook RB, eds. The major biogeochemical cycles and their interactions. Chichester: John Wiley & Sons, 67-113.

*Cuesta-Santos OA, Oritz-Bulto PL, Gozalez MLG. 1998. Deposition and atmospheric nitrogen concentrations trends in Cuba. Water Air Soil Pollut 106(1-2):163-169.

Cummings JH, Stephen AM, Branch WJ. 1981. Implications of dietary fiber breakdown in the human colon. Banbury Rep 7:71-81.

*da Fonseca J, Brito MJ, Freitas J, et al. 1998. Acute colitis caused by caustic products. Am J Gastroenterol 93(12):2601-2602.

*da Fonseca-Wollheim F. 1995. The influence of pH and various anions on the distribution of NH4+ in human blood. Eur J Clin Chem Clin Biochem 33(5):289-294.

*Dalhamn T. 1963. Effect of ammonia alone and combined with carbon particles on ciliary activity in the rabbit trachea in vivo, with studies of the absorption capacity of the nasal cavity. Int J Air Water Pollut 7:531-539.

Damm CJ, Lucas D, Sawyer RF, et al. 2001. Excimer laser fragmentation-fluorescence spectroscopy as a method for monitoring ammonium nitrate and ammonium sulfate particles. Chemosphere 42(5-7):655-661.

*Daubert TE, Danner RP. 1989. Physical and thermodynamic properties of pure chemicals: Data compilation. Washington, DC: Taylor & Francis.

*Davies BMA, Yudkin J. 1952. Studies in biochemical adaptation. The origin of urinary ammonia as indicated by the effect of chronic acidosis and alkalosis on some renal enzymes in the rat. Biochem J 52:407-412.

*Dawson GA. 1977. Atmospheric ammonia from undisturbed land. J Geophys Res 82(21):3125-3133.

*Dawson GA, Farmer JC. 1984. Highly soluble atmospheric trace gases in the Southwestern United States. I. Inorganic species: NH_3, HNO_3, SO_3. J Geophys Res 89(D3):4779-4787.

Debreczeni K, Berecz K. 1998. Monitoring of gaseous nitrogen losses from nitrogen fertilizers in model experiments. Commun Soil Sci Plant Anal 29(11-14):2207-2216.

De Datta SK. 1995. Nitrogen transformations in wetland rice ecosystems. Fert Res 42(1-3):193-203.

de Knegt RJ, Schalm SW, van der Rijt CC, et al. 1994. Extracellular brain glutamate during acute liver failure and during acute hyperammonemia simulating acute liver failure: An experimental study based on in vivo brain dialysis. J Hepatol 20(1):19-26.

*de la Hoz RE, Schlueter DP, Rom WN. 1996. Chronic lung disease secondary to ammonia inhalation injury: A report on three cases. Am J Ind Med 29(2):209-214.

*Demerec M, Bertani G, Flint J. 1951. A survey of chemicals for mutagenic action on E. coli. Am Nat 85:119-136.

9. REFERENCES

*Denmead OT, Freney JR, Simpson JR. 1982. Atmospheric dispersion of ammonia during application of anhydrous ammonia fertilizer. J Environ Qual 11:568-572.

*De Sousa RC, Harrington JT, Ricanati ES, et al. 1974. Renal regulation of acid-base equilibrium during chronic administration of mineral acid. J Clin Invest 53:465-476.

DeSutter TM, Clay SA, Clay DE. 1998. Atrazine, alachlor, and total inorganic nitrogen concentrations of winter wind-eroded sediment samples. J Environ Sci Health B 33(6):683-691.

*Diekman MA, Scheidt AB, Sutton AL, et al. 1993. Growth and reproductive performance, during exposure to ammonia, of gilts afflicted with pneumonia and atrophic rhinitis. Am J Vet Res 54(12):2128-2131.

*Dimmock NA, Marshall GB. 1986. The determination of free ammonia in ambient air with diffusion/denuder tubes. Anal Chim Acta 185:159-169.

*Dodd KT, Gross DR. 1980. Ammonia inhalation toxicity in cats: A study of acute and chronic respiratory dysfunction. Arch Environ Health 35:6-14.

*DOI. 1985. Nitrogen (ammonia). Bureau of mines Bulletin 675. Washington, DC: Department of the Interior.

*Doig PA, Willoughby RA. 1971. Response of swine to atmospheric ammonia and organic dust. J Am Vet Med Assoc 159:1353-1361.

Dolinska M, Hilgier W, Albrecht J. 1996. Ammonia stimulates glutamine uptake to the cerebral non-synaptic mitochondria of the rat. Neurosci Lett 213(1):45-48.

*Donham KJ. 1991. Association of environmental air contaminants with disease and productivity in swine. Am J Vet Res 52(10):1723-1730.

*Donham KJ, Popendorf WJ. 1985. Ambient levels of selected gases inside swine confinement buildings. Am Ind Hyg Assoc J 46:658-661.

*Donham KJ, Cumro D, Reynolds SJ, et al. 2000. Dose-response relationships between occupational aerosol exposures and cross-shift declines of lung function in poultry workers: recommendations for exposure limits. J Occup Environ Med 42(3):260-269.

*Donham KJ, Knapp LW, Monson R, et al. 1982. Acute toxic exposure to gases from liquid manure. J Occup Med 24:142-145.

*Donham KJ, Reynolds SJ, Whitten P, et al. 1995. Respiratory dysfunction in swine production facility workers: dose-response relationships of environmental exposures and pulmonary function. Am J Ind Med 27(3):405-418.

Dow SW, Fettman MJ, Smith KR, et al. 1990. Effects of dietary acidification and potassium depletion on acid-base balance, mineral metabolism and renal function in adult cats. J Nutr 120(6):569-578.

*Doyle GJ, Tuazon EC, Graham RA, et al. 1979. Simultaneous concentrations of ammonia and nitric acid in a polluted atmosphere and their equilibrium relationship to particulate ammonium nitrate. Environ Sci Technol 13:1416-1419.

Doyle J, Watts S, Solley D, et al. 2001. Exceptionally high-rate nitrification in sequencing batch reactors treating high ammonia landfill leachate. Water Sci Technol 43(3):315-322.

*Drummond JG, Curtis SE, Simon J, et al. 1980. Effects of aerial ammonia on growth and health of young pigs. J Anim Sci 50(6):1085-1091.

*Duda GD, Handler P. 1958. Kinetics of ammonia metabolism in vivo. J Biol Chem 232:303-314.

Dueck TA, Van der Eerden LJ. 2000. Interactions between climate change and nitrogen deposition, with emphasis on ammonia. In: Singh SN, ed. Trace gas emissions and plants. Dordrecht, The Netherlands: Kluwer Academic Publishers, 291-307.

Duke JA. 1977. Phytotoxin tables. CRC Crit Rev Toxicol 5:189-237.

Duke-Elder S, MacFaul PA. 1972. In: Duke-Elder S, ed. System of ophthalmology. Injuries. Non-mechanical injuries. St. Louis, MO: The C.V. Mosby Company, 1079-1085.

Duncan K, Jennings E, Hettenbach S, et al. 1998. Nitrogen cycling and nitric oxide emissions in oil-impacted prairie soils. Biorem J 1(3):195-208.

*Eaton WC, Rickman EE, Jayanty RKM, et al. 1996. Method 301 evaluation of a technique for collection and measurement of ammonia in stationary source emissions. Measurement of toxic and related air pollutants: Proceedings of an international specialty conference, May 7-9, 1996, Research Triangle Park, North Carolina. Pittsburgh, PA: Air and Waste Management Association, 583-588.

Edwards PJ, Kochenderfer JN, Seegrist DW. 1991. Effects of forest fertilization on stream water chemistry in the Appalachians. Water Resour Bull 27(2):265-274.

Effler SW, Brooks CM, Auer MT, et al. 1990. Free ammonia and toxicity criteria in a polluted urban lake. Res J Water Pollut Control Fed 62(6):771-779.

*Effler SW, Gelda RK, Matthews CM. 2001. Implications of industrial loads for ammonia pollution in an urban lake. Water Environ Res 73(2):192-203.

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

*Englande AJ, Smith JK, English JN. 1978. Potable water quality of advanced wastewater treatment plant effluents. Prog Water Technol 10:17-39.

*EPA. 1979. Effects of endogenous ammonia on neutralization of inhaled sulfuric acid aerosols. Cininnatti, OH: U.S. Environmental Protection Agency, Health Effects Research Lab. EPA600179045. PB80147978.

*EPA. 1980. Source category survey: Ammonia manufacturing industry. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality, EPA450380014.

*EPA. 1983. Methods for chemical analysis of water and wastes. Ammonia. U.S. Environmental Protection Agency. EPA600479020.

*EPA. 1987a. Extremely hazardous substances (EHS) chemical profiles and emergency first aid guides. Ammonia. U.S. Environmental Protection Agency. http://www.epa.gov/swercepp/ehs/ehslist.html. July 06, 2004.

*EPA. 1987b. Toxic air pollutant/source crosswalk–a screening tool for locating possible sources emitting air pollutants. ResearchTriangle Park, NC: U.S. Environmental Protection Agency. Code of Federal Regulations. EPA4504487023A.

EPA. 1988. Analysis of clean water act effluent guidelines pollutants: Summary of the chemicals regulated by industrial point source category. Washington, DC: U.S. Environmental Protection Agency. 40 CFR Parts 400-475.

*EPA. 1990. Interim methods for development of inhalation reference concentrations. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Office of Research and Development, Environmental Criteria and Assessment Office. EPA600890066A.

*EPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA600890066F.

*EPA. 1997a. Determination of ammonia in estuarine and coastal waters by gas segmented continuous flow colorimetric analysis. Method 349.0. U.S. Environmental Protection Agency.

*EPA. 1997b. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA630R96012.

*EPA. 2001a. Ammonia-N in water and biosolids by ion-selective electrode potentiometry with preliminary distillation. Method 1689. Washington, DC: U.S. Environmental Protection Agency. EPA821R01012.

*EPA. 2001b. Ammonia-N in water and biosolids by automated colorimetry with preliminary distillation. Method 1690. Washington, DC: U.S. Environmental Protection Agency. EPA821R01009.

*EPA. 2002a. Chemical accident prevention provisions. List of substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 68.130. Table 1. http://ecfr.access.gpo.gov/. May 02, 2002.

*EPA. 2002b. Chemical accident prevention provisions. Table of toxic endpoints. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 68. Appendix A. http://ecfrback.access.gpo.gov/. May 02, 2002.

*EPA. 2002c. Emergency planning and notification. The list of extremely hazardous substances and their threshold planning quantities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 355. Appendix A. http://ecfrback.access.gpo.gov/. May 02, 2002.

*EPA. 2002d. Superfund, emergency planning, and community right-to-know programs. Designation, reportable quantities, and notification. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4(a). http://ecfrback.access.gpo.gov/. May 02, 2002.

*EPA. 2002e. Tolerances and exemptions from tolerances for pesticide chemicals in food. Exemptions from the requirement of a tolerance. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.1001(c) and (d). http://ecfrback.access.gpo.gov/. May 02, 2002.

*EPA. 2002f. Tolerances and exemptions from tolerances for pesticide chemicals in food. Ammonia; exemption from the requirement of a tolerance. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.1003. http://ecfrback.access.gpo.gov/. May 02, 2002.

*EPA. 2002g. Toxic chemical release reporting: Community right-to-know. Chemicals and chemical categories to which this part applies. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65(a). http://ecfr.access.gpo.gov/. May 02, 2002.

*EPA. 2002h. Water programs. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4. Table A. http://ecfrback.access.gpo.gov/. May 02, 2002.

*EPA. 2002i. Water programs. Determination of reportable quantities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3. http://ecfrback.access.gpo.gov/. May 02, 2002.

*EPA. 2002j. Effluent guidelines and standards. CFR Title 40: Protection of Environment. U.S. Environmental Protection Agency. http://www.epa.gov/docs/epacfr40/chapt-I.info/subch-N.htm. May 31, 2002.

*EPA. 2004. Acute exposure guideline levels (AEGLs). Ammonia results. U.S. Environmental Protection Agency.

*EPIWIN. 2000. Ammonia. http://www.epa.gov/oppt/p2framework/docs/epiwin.htm. July 1, 2004.

Erisman J-W, Vermetten AWM, Asman WAH. 1988. Vertical distribution of gases and aerosols the behavior of ammonia and related components in the lower atmosphere. Atmos Environ 22(6):1153-1160.

*Erxleben H, Simon J, Moskvin LN, et al. 2000. Automized procedures for the determination of ozone and ammonia contents in air by using the chromatomembrane method for gas-liquid extraction. Fresenius J Anal Chem 336(4):332-335.

*Fangmeier A, Hadwiger-Fangmeier A, Van Der Eerden L, et al. 1994. Effects of atmospheric ammonia on vegetation: A review. Environ Pollut 86(1):43-82.

*Farmer JC, Dawson GA. 1982. Condensation sampling of soluble atmospheric trace gases. J Geophys Res 87(C11):8931-8942.

Farmer PM, Mulakkah T. 1990. The pathogenesis of hepatic encephalopathy. Ann Clin Lab Sci 20(2):91-97.

*Fazekas IG. 1939. Experimental suprarenal hypertrophy induced by ammonia. Endokrinologie 21:315-337.

FDA. 1973. GRAS (generally recognized as dafe) food ingredients - ammonium ion. U.S. Food and Drug Administration. PB221235.

9. REFERENCES

*FDA. 2001a. Direct food substances affirmed as generally recognized as safe. Ammonium chloride. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 184.1138. http://frwebgate.access.gpo.gov/. May 02, 2002.

*FDA. 2001b. Direct food substances affirmed as generally recognized as safe. Ammonium hydroxide. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 184.1139. http://frwebgate.access.gpo.gov/. May 02, 2002.

*FDA. 2001c. Direct food substances affirmed as generally recognized as safe. Ammonium sulfate. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 184.1143. http://frwebgate.access.gpo.gov/. May 02, 2002.

*FDA. 2001d. Drug products containing certain active ingredients offered over-the-counter. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 310.545(a). http://frwebgate.access.gpo.gov/. May 02, 2002.

*FDA. 2001e. Food additives permitted in feed and drinking water of animals. Anhydrous ammonia. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 573.180. http://frwebgate.access.gpo.gov/. May 02, 2002.

*FDA. 2001f. Substances generally recognized as safe. Ammonium hydroxide. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 582.1139. http://frwebgate.access.gpo.gov/. May 02, 2002.

*FDA. 2001g. Substances generally recognized as safe. Ammonium sulfate. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 582.1143. http://frwebgate.access.gpo.gov/. May 02, 2002.

*FEDRIP. 2002. Federal research in Progress. Dialog Information Services, Inc.

*FEDRIP. 2003. Federal research in Progress. Dialog Information Services, Inc.

*Felipo V, Butterworth RF. 2002. Neurobiology of ammonia. Prog Neurobiol 67:259-279.

*Felipo V, Grau E, Miñana MD, et al. 1993. Ammonium injection induces an *n*-methyl-d-aspartate receptor-mediated proteolysis of the microtubule-associated protein MAP-2. J Neurochem 60:1626-1630.

*Felipo V, Hermenegildo C, Montoliu C, et al. 1998. Neurotoxicity of ammonia and glutamate: molecular mechanisms and prevention. Neurotoxicology 19(4-5):675-681.

Felipo V, Miñana MD, Cabedo H, et al. 1994. L-Carnitine increases the affinity of glutamate for quisqualate receptors and prevents glutamate neurotoxicity. Neurochem Res 19(3):373-377.

Felipo V, Monfort P, Fernandez-Marticorena I, et al. 2000. Activation of NMDA receptors in rat brain in vivo following acute ammonia intoxication. Characterization by in vivo brain microdialysis. Eur J Neurosci 12(Suppl 11):40.

*Ferguson WS, Koch WC, Webster LB, et al. 1977. Human physiological response and adaption to ammonia. J Occup Med 19:319-326.

9. REFERENCES

*Fernandez JM, Croom WJ, Johnson AD, et al. 1988. Subclinical ammonia toxicity in steers: Effects on blood metabolite and regulatory hormone concentrations. J Anim Sci 66(12):3259-3266.

*Fernandez JM, Croom WJ, Tate LP, et al. 1990. Subclinical ammonia toxicity in steers: Effects on hepatic and portal-drained visceral flux of metabolites and regulatory hormones. J Anim Sci 68(6):1726-1742.

*Ferrier B, Martin M, Baverel G. 1988. Valproate-induced stimulation of renal production and excretion in the rat. J Clin Chem Clin Biochem 26:65-67.

Ferreira EB, Ceddia RB, Curi R, et al. 1998. Swimming-exercise increases the capacity of perfused rat liver to produce urea from ammonia and L-glutamine. Res Commun Mol Pathol Pharmacol 102(3):289-303.

Flessner MF, Wall SM, Knepper MA. 1992. Ammonium and bicarbonate transport in rat outer medullary collecting ducts. Am J Physiol 262(1 Pt 2):F1-F7.

*Flury KE, Dines DE, Rodarte JR, et al. 1983. Airway obstruction due to inhalation of ammonia. Mayo Clin Proc 58:389-393.

*Fox DL. 1987. Air pollution. Anal Chem 59:280R-294R.

Freedman LR, Beeson PB. 1961. Experimental pyelonephritis. VIII. The effect of acidifying agents on susceptibility to infection. Yale J Biol Med 33:318-332.

*Fürst P, Josephson B, Maschio G, et al. 1969. Nitrogen balance after intravenous and oral administration of ammonium salts to man. J Appl Phys 26:13-22.

*Gaafar H, Girgis R, Hussein M, et al. 1992. The effect of ammonia on the respiratory nasal mucosa of mice. A histological and histochemical study. Acta Otolaryngol (Stockh) 112(2):339-342.

Gad HA, El-Nasr ES, El-Naasan A, et al. 1994. The effect of some environmental conditions on the pregnant does and its maternal behavior. J Anim Sci 72(Suppl 1):155.

*Galbally IE. 1985. The emission of nitrogen to the remote atmosphere: Background paper. NATO ASI Ser C 159:27-53.

Galbally IE, Roy CR. 1983. The fate of nitrogen compounds in the atmosphere. Dev Plant Soil Sci 9:265-284.

Garcia MV, Lopez-Mediavilla C, Juanes de la Pena MC, et al. 2003. Tolerance of neonatal rat brain to acute hyperammonemia. Brain Res 973:31-38.

*Gay WMB, Crane CW, Stone WD. 1969. The metabolism of ammonia in liver disease: A comparison of urinary data following oral and intravenous loading of [^{15}N]ammonium lactate. Clin Sci 37:815-823.

*George A, Bang RL, Lari AR, et al. 2000. Liquid ammonia injury. Burns 26(4):409-413.

George JD, Fail PA, Grizzle TB, et al. 1993. Reproductive toxicity evaluation of a pesticide/fertilizer mixture administered in the drinking water to mice. Toxicologist 13(1):77.

9. REFERENCES

*Georgii HW, Gravenhorst G. 1977. The ocean as source or sink of reactive trace-gases. Pure Appl Geophys 115:503-511.

Gibson GE, Zimber A, Krook L, et al. 1971. Nucleic acids and brain and intestinal lesions in ammonia intoxicated mice [Abstract]. Fed Proc 30:578.

*Gilbert GJ. 1988. Acute ammonia intoxication 37 years after ureterosigmoidostomy. South Med J 81(11):1443-1445.

*Gilliam JW, Daniels RB, Lutz JF. 1974. Nitrogen content of shallow ground water in the North Carolina Coastal Plain. J Environ Qual 3(2):147-151.

Giroux M, Bremont F, Salles JP, et al. 2002. Exhaled NH_3 and excreted NH_4^+ in children in unpolluted or urban environments. Environ Int 28:197-202.

*Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect Suppl 101(2):65-71.

Goldman AS, Yakovac WC. 1964. Salicylate intoxication and congenital anomalies. Arch Environ Health 8:648-656.

*Gomzi M. 1999. Indoor air and respiratory health in preadolescent children. Atmos Environ 33(24-25):4081-4086.

*Gomzi M, Šarić M. 1997. Respiratory impairment among children living in the vicinity of a fertilizer plant. Int Arch Occup Environ Health 70(5):314-320.

*Goulding KWT, Bailey NJ, Bradbury NJ, et al. 1998. Nitrogen deposition and its contribution to nitrogen cycling and associated soil processes. New Phytol 139(1):49-58.

*Graedel TE. 1978. Inorganic nitrogen compounds: Emission and detection. In: Chemical compounds in the atmosphere. New York, NY: Academic Press, 19.

*Grant WM. 1974. Ammonia. In: Toxicology of the eye. 2nd edition. Springfield, IL: Charles C Thomas, 121-127.

*Greenberg AE, Trussell RR, Clesceri LS, eds. 1985. Nitrogen (ammonia) standard methods for the examination of water and wastewater. Washington, DC: American Public Health Association, American Water Works Association, Water Pollution Control Federation, 374-391.

Gregory JW, Beail N, Boyle NA, et al. 1989. Dietary treatment of hyperlysinemia. Arch Dis Child 64(5):716-720.

*Gupta BN, Khanna RN, Data KK. 1979. Toxicological studies of ammonium sulfamate in rat after repeated oral administration. Toxicology 13:45-49.

*Gustin P, Urbain B, Prouvost JF, et al. 1994. Effects of atmospheric ammonia on pulmonary hemodynamics and vascular permeability in pigs: Interaction with endotoxins. Toxicol Appl Pharmacol 125(1):17-26.

9. REFERENCES

*Guyton AC. 1981. The body fluids and kidneys. Textbook of medical physiology. Philadelphia: WB Saunders Company, 456-458, 889.

*Guzelian PS, Henry CJ, Olin SS, eds. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences Institute Press.

Hagiwara A, Shibata M, Kurata Y, et al. 1983. Long-term toxicity and carcinogenicity test of ammonia-process caramel colouring given to B6C3F1 mice in the drinking-water. Food Cosmet Toxicol 21:701-706.

*Harada K, Murawaki Y, Hirayama C. 1985. Comparative studies of nicotinohydroxamic acid and neomycin on ammonia and urea metabolism in rats. Res Commun Chem Pathol Pharmacol 49:309-312.

*Hargreaves JA. 1998. Nitrogen biogeochemistry of aquaculture ponds. Aquaculture 166(3-4):181-212.

*Harper LA, Sharpe RR. 1995. Nitrogen dynamics in irrigated corn: Soil-plant nitrogen and atmospheric ammonia transport. Agron J 87(4):669-675.

Harrison RM, Sturges WT, Kitto A-MN, et al. 1990. Kinetics of evaporation of ammonium chloride and ammonium nitrate aerosols. Atmos Environ 24(7):1883-1888.

*Harward CN, McClenny WA, Hoell JM, et al. 1982. Ambient ammonia measurements in coastal Southeastern Virginia. Atmos Environ 16(10):2497-2500.

Hatch DJ, Jarvis SC, Dollard GJ. 1990. Measurements of ammonia emission from grazed grassland. Environ Pollut 65(4):333-346.

*Hatton DV, Leach CS, Beaudet AL, et al. 1979. Collagen breakdown and ammonia inhalation. Arch Environ Health 34:83- 86.

*Hauser JR. 1984. Use of water hyacinth aquatic treatment systems for ammonia control and effluent polishing. J Water Pollut Control Fed 56(3):219-225.

Hawkins PA, DeJoseph MR, Hawkins RA. 1996. Eliminating metabolic abnormalities of portacaval shunting by restoring normal liver blood flow. Am J Physiol 270(6 PT 1):E1037-E1042.

Hawkins RA, Miller AL, Nielsen RC, et al. 1973. The acute action of ammonia on rat brain metabolism *in vivo*. Biochem J 134:1001-1008.

*HazDat. 2004. HazDat Database: ATSDR's Hazardous Substance Release and Health Effects Database. Atlanta, GA: Agency for Toxic Substances and Disease Registry. www.atsdr.cdc.gov/hazdat.html. July 02, 2004.

Hazell AS, Norenberg MD. 1996. Ammonia and manganese increase arginine uptake in cultured astrocytes. J Neurochem 66(Suppl 1):S69.

Hazell AS, Norenberg MD. 1998. Ammonia and manganese increase arginine uptake in cultured astrocytes. Neurochem Res 23(6):869-873.

*Heederik D, Brouwer R, Biersteker K, et al. 1991. Relationship of airborne endotoxin and bacteria levels in pig farms with the lung function and respiratory symptoms of farmers. Int Arch Occup Environ Health 62(8):595-601.

*Heederik D, van Zwieten R, Brouwer R. 1990. Across-shift lung function changes among pig farmers. Am J Ind Med 17(1):57-58.

*Hegg DA, Radke LF, Hobbs PV, et al. 1987. Nitrogen and sulfur emissions from the burning of forest products near large urban areas. J Geophys Res 92:701-714.

*Hegg DA, Radke LF, Hobbs PV. 1988. Ammonia emissions from biomass burning. Geophys Res Lett 15(4):335-337.

*Heifer U. 1971. [Casuistic contribution to acute lethal inhalation poisoning by ammonia.] Lebensversicherungsmedizin 22:60-62. (German)

Heindel JJ, Chapin RE, Gulati DK, et al. 1994. Assessment of the reproductive and developmental toxicity of pesticide/fertilizer mixtures based on confirmed pesticide contamination in California and in Iowa groundwater. Fundam Appl Toxicol 22:605-621.

Heindel JJ, George JD, Fail PA, et al. 1997. Reproductive toxicology. Pesticide/fertilizer mix III (Iowa). Environ Health Perspect Suppl 105(Suppl 1):375-376.

Heindel JJ, Price CJ, George JD, et al. 1992. Developmental toxicity evaluation in rats of a pesticide/fertilizer mixture selected to mimic environmental exposure. Teratology 45(5):500.

*Helmers S, Top FH, Knapp LW. 1971. Ammonia injuries in agriculture. J Iowa Med Soc 61:271-280.

*Henderson Y, Haggard HW. 1927. Group II. Irritant gases, their action, acute and chronic, and sequelae. Noxious gases and the principles of respiration influencing their action. New York: Chemical Catalog Company.

*Henry RJ. 1964. Non-protein nitrogenous constituents. In: Clinical chemistry principles and technics. Los Angeles, CA: Harper & Row, 325-331.

Herbst E, DeFrees DJ, Talbi D, et al. 1991. Calculations on the rate of the ion-molecule reaction between NH3+ and H2. J Chem Phys 94(12):7842-7849.

Hermenegildo C, Marcaida G, Montoliu C, et al. 1996. NMDA receptor antagonists prevent acute ammonia toxicity in mice. Neurochem Res 21(10):1237-1244.

Hermenegildo C, Monfort P, Felipo V. 2000. Activation of N-methyl-d-aspartate receptors in rat brain in vivo following acute ammonia intoxication: Characterization by in vivo brain microdialysis. Hepatology 31(3):709-715.

*Herrera L, Kazemi H. 1980. Interaction between ammonia and CO_2 as ventilatory stimulants. Bull Eur Physiopathol Respir 16:459-468.

*Hilado CJ, Casey CJ, Furst A. 1977. Effect of ammonia on swiss albino mice. J Combust Toxicol 4:385-388.

9. REFERENCES

*Hilado CJ, Cumming HG, Machado AM, et al. 1978. Effect of individual gaseous toxicants on mice. Proc West Pharmacol Soc 21:159-160.

*Hindfelt B, Plum F. 1975. L-methionine DL-sulphoximine and acute ammonia toxicity. J Pharm Pharmacol 27:456-458.

Hindfelt B, Siesjo BK. 1971. Cerebral effects of acute ammonia intoxication II. The effect upon energy metabolism. Scand J Clin Lab Invest 28:365-374.

*Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. J Natl Cancer Inst 84(5):313-320.

*Hoff JD, Nelson DW, Sutton AL. 1981. Ammonia volatization from liquid swine manure applied to cropland. J Environ Qual 10(1):90-95.

*Holness DL, Purdham JT, Nethercott JR. 1989. Acute and chronic respiratory effects of occupational exposure to ammonia. Am Ind Hyg Assoc J 50(12):646-650.

*HSDB. 2003. Ammonia. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. June 27, 2004.

Huddleston GM, Gillespie WB, Rodgers JH. 2000. Using constructed wetlands to treat biochemical oxygen demand and ammonia associated with a refinery effluent. Ecotoxicol Environ Saf 45(2):188-193.

Hunt RD. 1977. Measurement of partial pressure of ammonia in breath and arterial blood: evidence for secretion of ammonia into expired gas by metabolism of monoamines in the lung. Diss Abstr Int B 37:3279.

*Huizenga JR, Tangerman A, Gips CH. 1994. Determination of ammonia in biological fluids. Ann Clin Biochem 31(6):529-543.

*Huizenga JR, Gips CH, Tangerman A. 1996. The contribution of various organs to ammonia formation: A review of factors determining the arterial ammonia concentration. Ann Clin Biochem 33:23-30.

Hultberg B, Isaksson A, Bugge M. 1988. The effect of porta-caval shunt ammonia infusion and alcohol administration on rat plasma beta hexosaminidase. Liver 8(3):129-131.

*Hutchinson GL, Viets FG. 1969. Nitrogen enrichment of surface water by absorption of ammonia volatilized from cattle feedlots. Science 166:514-515.

*Hutchinson GL, Mosier AR, Andre CE. 1982. Ammonia and amine emissions from a large cattle feedlot. J Environ Qual 11:288-293.

Hytonen M, Leino T, Sala E, et al. 1997. Nasal provocation test in the diagnostics of hairdressers' occupational rhinitis. Acta Otolaryngol Suppl (Stockh) 529:133-136.

*IBT. 1974. Irritation threshold evaluation study with ammonia. Report to International Institute of Ammonia Refrigeration by Industrial Biotest Laboratories, Inc. 663-03161. (as cited in NIOSH 1974)

9. REFERENCES

*Iles JF, Jack JJB. 1980. Ammonia: Assessment ofits action on postsynaptic inhibition as a cause of convulsions. Brain 103:555-578.

Ilies P, Mavinic DS. 2001. A pre- and post-denitrification system treating a very high ammonia landfill leachate: Effects of pH change on process performance. Environ Technol 22(3):289-300.

*Industrial Bio-Test Laboratories, Inc. 1973. Irritation threshold evaluation study with ammonia. Report to international institute of ammonia refrigeration (IBT No. 663-03160). Northbrook, Il: Industrial Bio-Test Laboratories, Inc.

*IRIS. 2004. Integrated Risk Information System. http://www.epa.gov/iris. May 02, 2002.

*Irwin JG, Williams NL. 1988. Acid rain: Chemistry and transport. Environ Pollut 50:29-59.

Itzhak Y, Norenberg MD. 1994. Attenuation of ammonia toxicity in mice by PK 11195 and pregnenolone sulfate. Neurosci Lett 182(2):251-254.

*Iwaoka WT, Krone CA, Sullivan JJ, et al. 1981. Effect of pH and ammonium ions on mutagenic activity in cooked beef. Cancer Lett 12:335-341.

*Izumi H, Karita K. 1993. Reflex vasodilatation in the cat lip elicited by stimulation of nasal mucosa by chemical irritants. Am J Physiol 265(4 Pt 2):R733-R738.

Jaffe HL, Bodansky A, Blair JE. 1932. The effects of parathormone and ammonium chloride on the bones of rabbits. J Exp Med 55:695-701.

*Janicki RH. 1970. Renal adaptation during chronic NH_4Cl acidosis in the rat: No role for hyperplasia. Am J Physiol 219:613-618.

*Jarudi MD, Golden MD. 1973. Ammonia eye injuries. J Iowa Med Soc 63:260-263.

*Jeffers LJ, Dubow RA, Zieve L, et al. 1988. Hepatic encephalopathy and orotic aciduria associated with hepatocellular carcinoma in a noncirrhotic liver. Hepatology 8(1):78-81.

*Jin H, Yang X, Yu H, et al. 1999. Identification of ammonia and volatile phenols as primary toxicants in a coal gasification effluent. Bull Environ Contam Toxicol 63(3):399-406.

*Jingsheng C, Xuemin G, Dawei H, et al. 2000. Nitrogen contamination in the Yangtze river system, China. J Hazard Mater 73(2):107-113.

*Johnson CA, Sigg L, Zobrist J. 1987. Case studies on the chemical composition of fogwater: The influence of local gaseous emissions. Atmos Environ 21(11):2365-2374.

Johnson L. 1975. The effects of anhydrous ammonia on the environment and its direct effect on humans. J Environ Health 37:462-465.

*Jones JG, Simon BM, Horsley RW. 1982. Microbiological sources of ammonia in freshwater lake sediments. J Gen Microbiol 128:2823-2831.

Jones RD, Schwab AP. 1993. Nitrate leaching and nitrite occurrence in a fine-textured soil. Soil Sci 155(4):272-282.

*Jones W, Morring K, Olenchock SA, et al. 1984. Environmental study of poultry confinement buildings. Am Ind Hyg Assoc J 45(11):760-766.

*Kalandarov S, Bychkov VP, Frenkel ID, et al. 1984. [Effect of an increased ammonia content in an enclosed atmosphere on the adrenocortical system in man.] Kosm Biol Aviakosm Med 18:75-77. (Russian)

Kamin H, Handler P. 1957. Amino acid and protein metabolism. Annu Rev Biochem 26:419-490.

Kanamori K, Ross BD, Chung JC, et al. 1996. Severity of hyperammonemic encephalopathy correlates with brain ammonia level and saturation of glutamine synthetase in vivo. J Neurochem 67(4):1584-1594.

Kapeghian JC, Jones AB, Waters IW. 1985. Effects of ammonia on selected hepatic microsomal enzyme activity in mice. Bull Environ Contam Toxicol 35:15-22.

*Kapeghian JC, Mincer HH, Jones AL, et al. 1982. Acute inhalation toxicity of ammonia in mice. Bull Environ Contam Toxicol 29:371-378.

*Kass I, Zamel N, Dobry CA, et al. 1972. Bronchiectasis following ammonia burns of the respiratory tract. Chest 62(3):282-285.

*Kauppinen T. 1986. Occupational exposure to chemical agents in the plywood industry. Ann Occup Hyg 30(1):19-29.

*Kawano S, Tsujii M, Fusamoto H, et al. 1991. Chronic effect of intragastric ammonia on gastric mucosal structures in rat. Dig Dis Sci 36(1):33-38.

*Kelly TJ, Tanner RL, Newman L, et al. 1984. Trace gas and aerosol measurements at a remote site in the Northeast U.S. Atmos Environ 18(12):2565-2576.

*Kemp MK, Dodds WK. 2002. The influence of ammonium, nitrate, and dissolved oxygen concentrations on uptake, nitrification, and denitrification rates associated with prairie stream substrata. Limnol Oceanogr 47(5):1380-1393.

Kerr LA, McCoy CP, Boyle CR, et al. 1990. Effects of ammoniation of endophyte fungus-infested fescue hay on serum prolactin concentration and rectal temperature in beef cattle. Am J Vet Res 51(1):76-78.

*Kerstein MD, Schaffzin DM, Hughes WB, et al. 2001. Acute management of exposure to liquid ammonia. Mil Med 166(10):913-914.

Khera KS. 1991a. Chemically-induced alterations in maternal homeostasis and conceptal histology: their etiologic significance in rat fetal anomalies [Abstract]. Teratology 43(5):414.

Khera KS. 1991b. Chemically induced alterations in maternal homeostasis and histology of conceptus: their etiologic significance in rat fetal anomalies. Teratology 44(3):259-297.

*Kienzle E, Wilms-Eilers S. 1994. Struvite diet in cats: effect of ammonium chloride and carbonates on acid base balance of cats. J Nutr 124(Suppl 12):2652S-2659S.

9. REFERENCES

*Kimura T, Budka H. 1986. Glial fibrillary acidic protein and S-100 protein in human hepatic encephalopathy: Immunocytochemical demonstration of dissociation of two glia associated proteins. Acta Neuropathol 70:17-21.

*Kirchner M, Braeutigam S, Ferm M, et al. 1999. Field intercomparison of diffusive samplers for measuring ammonia. J Environ Monitor 1(3):259-265.

*Klein J, Olson KR, McKinney HE. 1985. Caustic injury from household ammonia. Am J Emerg Med 3:320.

*Kleinman MT, Hyde DM, Bufalino C, et al. 2003. Toxicity of chemical components of fine particles inhaled by aged rats: Effects of concentration. J Air Waste Manage Assoc 53:1080-1087.

*Klendshoj NC, Rejent TA. 1966. Tissue levels of some poisoning agents less frequently encountered. J Forensic Sci 11(1):75-80.

Kligerman AD, Chapin RE, Erexson GL, et al. 1993. Analyses of cytogenetic damage in rodents following exposure to simulated groundwater contaminated with pesticides and a fertilizer. Mutat Res 300(2):125-134.

Knapka JJ, Smith KP, Judge FJ. 1977. Effect of crude fat and crude protein on reproduction and weanling growth in four strains of inbred mice. J Nutr 107:61-69.

*Knapp KT, Durham JL, Ellestad TG. 1986. Pollutant sampler for measurements of atmospheric acidic dry deposition. Environ Sci Tech 20:633-637.

*Koenig H, Koenig R. 1949. Production of acute pulmonary edema by ammonium salts. Proc Soc Exp Biol Med 70(3):375-380.

Konsenko E, Felip V, Minana MD, et al. 1991. Ammonium ingestion prevents depletion of hepatic energy metabolites induced by acute amonium intoxication. Arch Biochem Biophys 290(2):484-488.

*Konsenko E, Kaminsky YG, Felipo V, et al. 1993. Chronic hyperammonemia prevents changes in brain energy and ammonia metabolites induced by acute ammonium intoxication. Biochim Biophys Acta 1180(3):321-326.

*Kosenko E, Kaminisky Y, Grau E, et al. 1994. Brain ATP depletion induced by acute ammonia intoxication in rats is mediated by activation of the NMDA receptor and Na+, K(+)-ATPase. J Neurochem 63(6):2172-2178.

Kosenko E, Kaminsky Y, Grau E, et al. 1995. Nitroarginine, an inhibitor of nitric oxide synthetase, attenuates ammonia toxicity and ammonia-induced alterations in brain metabolism. Neurochem Res 20(4):451-456.

Kosenko E, Kaminiski Y, Lopata O, et al. 1999. Blocking NMDA receptors prevents the oxidative stress induced by acute ammonia intoxication. Free Radic Biol Med 22(11/12):1369-1374.

Kosenko E, Llansola M, Montoliu C. 2003a. Glutamine synthetase activity and glutamine content in brain: modulation by NMDA receptors and nitric oxide. Neurochem Int 43:493-499.

Kosenko E, Venediktova N, Kaminsky Y, et al. 2003b. Sources of oxygen radicals in brain in acute ammonia intoxication in vivo. Brain Res 981:193-200.

Koyuncuoglu H, Keyer M, Simsek S, et al. 1978. Ammonia intoxication: Changes of brain levels of putative neurotransmitters and related compounds and its relevance to hepatic coma. Pharmacol Res Commun 10(9):787-807.

*Krajenbrink GJW, Ronen D, Van Duijvenbooden W, et al. 1988. Monitoring of recharge water quality under woodland. J Hydrol 98:83-102.

*Kramer DA. 2000. Nitrogen. U.S. Geological survey minerals yearbook. http://minerals.usgs.gov/minerals/pubs/commodity/nitrogen/480400.pdf. June 05, 2001.

*Kramer DA. 2002. Nitrogen (fixed)–ammonia. U.S. Geological survey, mineral commodity summaries. http://minerals.usgs.gov/minerals/pubs/commodity/nitrogen/480302.pdf. July 06, 2002.

Kramer DA. 2003. Nitrogen. U.S. Geological survey minerals yearbook. http://minerals.usgs.gov/minerals/pubs/commodity/nitrogen/nitromyb02.pdf. July 19, 2003.

Kramer DA. 2004. Nitrogen (fixed)–ammonia. U.S. Geological survey, mineral commodity summaries. http://minerals.usgs.gov/minerals/pubs/commodity/nitrogen/nitromcs04.pdf. June 15, 2004.

*Kretzschmar HA, DeArmond SJ, Forno LS. 1985. Measurement of GFAP in hepatic encephalopathy by ELISA and transblots. J Neuropathol Exp Neurol 44:459-471.

*Krishnan K, Andersen ME. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. 3rd ed. New York, NY: Raven Press, Ltd., 149-188.

*Krishnan K, Andersen ME, Clewell HJ III, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures: Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

*Kucey RMN. 1988. Ammonia loss following surface application of urea fertilizers to a calcareous soil. Commun Soil Sci Plant Anal 19(4):431-445.

Kukkonen J, Savolainen AL, Valkama I, et al. 1993. Long-range transport of ammonia released in a major chemical accident at Ionava, Lithuania. J Hazard Mater 35(1):1-16.

Kullman GJ, Thorne PS, Waldron F, et al. 1998. Organic dust exposures from work in dairy barns. Am Ind Hyg Assoc J 59:403-413.

*Kumar S. 1985. An eulerian model for scavenging of pollutants by raindrops. Atmos Environ 19(5):769-778.

*Kupprat I, Johnson RE, Hertig BA. 1976. Ammonia: A normal constituent of expired air during rest and exercise. Fed Proc 35:478.

Kuta CC, Maickel RP, Borowitz JL. 1984. Modification of drug action by hyperammonemia. J Pharmacol Exp Ther 229:85-90.

9. REFERENCES

*Lamar C. 1970. Ammonia toxicity in rats: Protection by α-methylglutamic acid. Toxicol Appl Pharmacol 17:795-803.

*Landahl HD, Herrmann RG. 1950. Retention of vapors and gases in the human nose and lung. Arch Ind Hyg Occup Med 1:36-45.

*Lane M, Gardner DK. 1994. Increase in postimplantation development of cultured mouse embryos by amino acids and induction of fetal retardation and exencephaly by ammonium ions. J Reprod Fertil 102(2):305-312.

*Langland M. 1992. Atmospheric deposition of ammonia from open manure-storage lagoons in south-central Pennsylvania. Environ Professional 14:28-37.

Larsen FS, Gottstein J, Blei AT. 2001. Cerebral hyperemia and nitric oxide synthase in rats with ammonia-induced brain edema. J Hepatol 34(4):548-554.

*Larson T, Frank R, Covert D, et al. 1980. The chemical neutralization of inhaled sulfuric acid aerosol. Am J Ind Med 1:449-452.

Last JA. 1989. Effects of inhaled acids on lung biochemistry. Environ Health Perspect 79:115-119.

*Latenser BA, Lucktong TA. 2000. Anhydrous ammonia burns: Case presentation and literature review. J Burn Care Rehab 21(1 PT 1):40-42.

*Lau N-C, Charlson RJ. 1977. On the discrepancy between background atmospheric ammonia gas measurements and the existence of acid sulfates as a dominant atmospheric aerosol. Atmos Environ 11:475-478.

*LeBlanc JR, Madhavan S, Porter RE. 1978. Ammonia. In: Grayson M, Eckroth D, eds. Kirk-Othmer encyclopedia of chemical technology. 3rd ed. Vol. 2. New York, NY: John Wiley & Sons, Inc., 470-516.

*Leduc D, Gris P, Lheureux P, et al. 1992. Acute and long term respiratory damage following inhalation of ammonia. Thorax 47(9):755-757.

*Lee DS, Bouwman AF, Asman WAH, et al. 1997. Emissions of nitric oxide, nitrous oxide and ammonia from grasslands on a global scale. In: Jarvis SC, Pain BF, eds. Gaseous nitrogen emissions from grasslands. New York, NY: Cab International, 353-371.

*Lee HS, Chan CC, Tan KT, et al. 1993. Burnisher's asthma-a case due to ammonia from silverware polishing. Singapore Med J 34(6):565-566.

Lee JH, Kim WH, Cho H, et al. 1998. N-carbamoyl-L-glutamate plus L-arginine can protect ammonia intoxication in rats with reduced functional liver mass. Biochem Biophys Res Commun 248(2):391-394.

Lee WM, Huang WM, Chen YY. 2001. Effect of relative humidity on mixed aerosols in atmosphere. J Environ Sci Health Part A 36(4):533-544.

*Legters L, Morton JD, Nightingale TE, et al. 1981. Biological effects of short, high-level exposure to gases: Ammonia, carbon monoxide, sulfur dioxide and nitrogen oxides: Final summary report. Fort Detrick, MD: U.S. Army Medical Research and Development Command.

9. REFERENCES

*Lehninger AL. 1975. Biochemistry: The molecular basis of cell structure and function. 2nd ed. New York: Worth Publishers, Inc., 579-585.

Lemann J, Litzow JR, Lennon EJ. 1966. The effects of chronic acid loads in normal man: Further evidence for the participation of bone mineral in the defense against chronic metabolic acidosis. J Clin Invest 45(10):1608-1614.

*Leonard JJ, Feddes JJR, McQuitty JB. 1984. Air quality in commercial broiler housing. Can Agric Eng 26(1):65-72.

Leonard KM, Swanson GW. 2001. Comparison of operational design criteria for subsurface flow constructed wetlands for wastewater treatment. Water Sci Technol 43(11):301-307.

*Leonardos G, Kendall D, Barnard N. 1969. Odor threshold determinations of 53 odorant chemicals. J Air Pollut Control Assoc 19:91-95.

*Leung H-W. 1993. Physiologically-based pharmacokinetic modelling. In: Ballentine B, Marro T, Turner P, eds. General and applied toxicology. Vol. 1. New York, NY: Stockton Press, 153-164.

*Levine JS, Augustsson TR, Hoell JM. 1980. The vertical distribution of tropospheric ammonia. Geophys Res Lett 7(5):317-320.

*Levy DM, Divertie MB, Litzow TJ, et al. 1964. Ammonia burns of the face and respiratory tract. JAMA 190(10):95-98.

*Liao CM, Bundy DS. 1995. Quantification of ventilation on distribution of gaseous pollutants emitted from stored swine manure. J Environ Sci Health B 30(6):859-893.

Lide DR, ed. 1988. CRC handbook of chemistry and physics. 68th ed. Boca Raton, FL: CRC Press, Inc., 4-39.

*Lide DR, ed. 1998. CRC handbook of chemistry and physics. 79th ed. Boca Raton, FL: CRC Press, Inc.

*Liebhardt WC, Golt C, Tupin J. 1979. Nitrate and ammonium concentrations of ground water resulting from poultry manure applications. J Environ Qual 8(2):211-215.

Lin S, Raabe W. 1985. Ammonia intoxication: Effects on cerebral cortex and spinal cord. J Neurochem 44:1252-1258.

Lipsky RH, Vemuri MC, Silverman SJ. 1988. Changes in nuclear proteins of astrocytes as a result of acute ammonia or ethanol exposure. Neurochem Int 12(4):519-524.

*Livingston, AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4:301-324.

*Llansola M, Erceg S, Hernandez-Viadel M. 2002. Prevention of ammonia and glutamate neurotoxicity by carnitine: molecular mechanisms. Metab Brain Dis 17(4):389-397.

9. REFERENCES

*Lobasov M, Smirnov F. 1934. On the nature of the action of chemical agents on mutational process in drosophila melanogaster. II. The effect of ammonia on the occurrence of lethal transgenations. C R Seances Acad Sci Roum 3:177-178.

Lobley GE, Connell A, Lomax MA, et al. 1995. Hepatic detoxification of ammonia in the ovine liver: possible consequences for amino acid catabolism. Br J Nutr 73(5):667-685.

*Lopez G, Dean BS, Krenzelok EP. 1988. Oral exposure to ammonia inhalants: A report of 8 cases. Vet Hum Toxicol 30:350.

*Lotspeich WD. 1965. Renal hypertrophy in metabolic acidosis and its relation to ammonia excretion. Am J Physiol 208:1135-1142.

Lu Y, Wassmann R, Neue HU, et al. 2000. Dissolved organic carbon and methane emissions from a rice paddy fertilized with ammonium and nitrate. J Environ Qual 29(6):1733-1740.

*MacCarthy P, Klusman RW, Rice JW. 1987. Water analysis. Anal Chem 59:308R-337R.

*MacEwen JD, Vernot EH. 1972. Toxic hazards research unit - annual technical report. Wright Patterson AFB, OH: Aerospace Medical Research Laboratory, AD755358. AMRLTR7262, 70-73.

*MacEwen JD, Theodore J, Vernot EH. 1970. Human exposure to EEL concentrations of monomethylhydrazine. In: Proceedings 1st annual conference on environmental toxicology Wright-Patterson Air Force Base, OH: Aerospace Medical Research Laboratory. AMRLTR70102, 355-363.

*Mahendrappa MK. 1982. Effects of SO_2 pollution on nitrogen transformation in some organic soils of northeastern New Brunswick: Ammonia volatilization. Can J For Res 12:458-462.

*Malcolm SJ, Battersby NS, Stanley SO, et al. 1986. Organic degradation, sulphate reduction and ammonia production in the sediments of Loch Eil, Scotland. Estuarine Coastal Shelf Sci 23:689-706.

*Manninen A. 1988. Analysis of airborne ammonia: Comparison of field methods. Ann Occup Hyg 32(3):399-404.

*Manninen ATA, Savolainen H. 1989. Effect of short-term ammonia inhalation on selected amino acids in rat brain. Pharmacol Toxicol 64(3):244-246.

Manninen A, Anttila S, Savolainen H. 1988. Rat metabolic adaptation to ammonia inhalation. Proc Soc Exp Biol Med 187(3):278-281.

*Marcaggi P, Coles JA. 2001. Ammonium in nervous tissue: transport across cell membranes, fluxes from neurons to glial cells, and role in signalling. Prog Neurobiol 64:157-183.

*Marcaida G, Felipo V, Hermenegildo C, et al. 1992. Acute ammonia toxicity is mediated by the NMDA type of glutamate receptors. FEBS Lett 296(1):67-68.

Marconi AM, Battaglia FC, Meschia G, et al. 1989. A comparison of amino acid arteriovenous differences across the liver and placenta of the fetal lamb. Am J Physiol 257(6 Pt 1):E909-E915.

Martinelle K, Haggstrom L. 1993. Mechanisms of ammonia and ammonium ion toxicity in animal cells: Transport across cell membranes. J Biotechnol 30(3):339-350.

*Maswoswe SM, Cyr DM, Griffith AD, et al. 1986. The effect of sodium benzoate on ammonia toxicity in rats. Biochem Biophys Res Commun 138(1):369-373.

Matkowskyj KA, Marrero JA, Carroll RE, et al. 1999. Azoxymethane-induced fulminant hepatic failure in C57BL/6J mice: characterization of a new animal model. Am J Physiol 277(2 PT 1):G455-G462.

Matsuoka M, Igisu H. 1993. Comparison of the effects of L-carnitine, D-carnitine and acetyl-L-carnitine on the neurotoxicity of ammonia. Biochem Pharmacol 46(1):159-164.

Matsuoka M, Igisu H, Kohriyama K, et al. 1991. Suppression of neurotoxicity of ammonia by L-carnitine. Brain Res 567(2):328-331.

*Matthews DA, Effler SW, Matthews CM. 2000. Ammonia and toxicity criteria in polluted Onondaga Lake, New York. Water Environ Res 72(6):731-741.

Mautz WJ, Kleinman MT, Bhalla DK, et al. 2001. Respiratory tract responses to repeated inhalation of an oxicant and acid gas-particle air pollutant mixture. Toxicol Sci 61(2):331-341.

*Mayan MH, Merilan CP. 1972. Effects of Ammonia inhalation on respiration rate of rabbits. J Anim Sci 34:448-452.

Mayan MH, Merilan CP. 1976. Effects of ammonia inhalation on young cattle. N Z Vet J 24:221-224.

*Mayr U, Butsch A, Schneider S. 1992. Validation of two in vitro test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74:135-149.

McBurney MI, Van Soest PJ, Jeraci JL. 1987. Colonic carcinogenesis: the microbial feast or famine mechanism. Nutr Cancer 10:23-28.

McCandless DW. 1981. Metabolic turnover in the reticular activating system in ammonia induced coma. Neurobehav Toxicol Teratol 3:257-260.

McCandless DW, Schenker S. 1981. Effect of acute ammonia intoxication on energy stores in the cerebral reticular activating system. Exp Brain Res 44:325-330.

McCandless DW, Looney GA, Modak AT, et al. 1985. Cerebral acetylcholine and energy metabolism changes in acute ammonia intoxication in the lower primate Tupaia glis. J Lab Clin Med 106:183-186.

McCubbin DR, Apelberg BJ, Roe S, et al. 2002. Livestock ammonia management and particulate-related health benefits. Environ Sci Technol 36(6):1141-1146.

*McGuinness R. 1969. Ammonia in the eye. Br Med J 2:575.

McKhann GM, Tower DB. 1961. Ammonia toxicity and cerebral oxidative metabolism. Am J Physiol 200:420-424.

McKinney PE, Brent J, Kulig K. 1994. Acute zinc chloride ingestion in a child: Local and systemic effects. Ann Emerg Med 23(6):1383-1387.

Megarbane B, Bruneel F, Bedos JP, et al. 2000. Ammonium chloride poisoning: a misunderstood cause of metabolic acidosis with normal anion gap. Intensive Care Med 26(12):1869.

*Mégraud F, Neman-Simha V, Brugmann D. 1992. Further evidence of the toxic effect of ammonia produced by Helicobacter pylori urease on human epithelial cells. Infect Immun 60(5):1858-1863.

*Melbostad E, Eduard W. 2001. Organic dust-related respiratory and eye irritation in Norwegian farmers. Am J Ind Med 39(2):209-217.

*Metges CC, Petzke KH, El-Khoury AE, et al. 1999. Incorporation of urea and ammonia ntrogen into ileal and fecal microbial proteins and plasma free amino acids in normal men and ileostomates. Am J Clin Nutr 70(6):1046-1058.

*Meybeck M. 1982. Carbon, nitrogen, and phosphorus transport by world rivers. Am J Sci 282:401-450.

*Meyerhoff ME, Robins RH. 1980. Disposable potentiometric ammonia gas sensors for estimation of ammonia in blood. Anal Chem 52(14):2383-2387.

Michaels RA. 1999. Emergency planning and the cute toxic potency of inhaled ammonia. Environ Health Perspect 107(8):617-627.

Michoudet C, Chauvin MF, Baverel G. 1994. Glutamine synthesis from glucose and ammonium chloride by guinea-pig kidney tubules. Biochem J 297:69-74.

*Millea TP, Kucan JO, Smoot EC. 1989. Anhydrous ammonia injuries. J Burn Care Rehab 10(5):448-453.

Miñana MD, Felipo V, Grisolia S. 1988. Protective effect of long term ammonium ingestion against acute ammonium intoxication. Biochem Biophys Res Commun 153(3):979-983.

*Miñana MD, Felipo V, Grisolia S. 1989a. Assembly and disassembly of brain tubulin is affected by high ammonia levels. Neurochem Res 14(3):235-238.

*Miñana MD, Felipo V, Quel A, et al. 1989b. Selective regional distribution of tubulin induced in cerebrum by hyperammonemia. Neurochem Res 14(12):1241-1243.

Miñana MD, Hermenegildo C, Llsansola M, et al. 1996. Carnitine and choline derivatives containing a trimethylamine group prevent ammonia toxicity in mice and glutamate toxicity in primary cultures of neurons. J Pharmacol Exp Ther 279(1):194-19.

*Miñana MD, Marcaida G, Grisolia S, et al. 1995. Prenatal exposure of rats to ammonia impairs NMDA receptor function and affords delayed protection against ammonia toxicity and glutamate neurotoxicity. J Neuropathol Exp Neurol 54(5):644-650.

Minelli A, Lyons S, Nolte C, et al. 2000. Ammonium triggers calcium elevation in cultured mouse microglial cells by initiating Ca2+ release from thapsigargin-sensitive intracellular stores. Pflugers Arch 439(3):370-377.

9. REFERENCES

*Mishra S, Singh V, Jain A, et al. 2001. Simultaneous determination ammonia, aliphatic amines, aromatic amines and phenols at microgram 1-1 levels in environmental waters by solid-phase extraction of their benzoyl derivatives and gas chromatography-mass spectrometry. Analyst 126(10):1663-1668.

*Mitz SV, Giesy JP. 1985. Sewage effluent biomonitoring. II. Biochemical indicators of ammonia exposure in channel catfish. Ecotoxicol Environ Saf 10:40-52.

*Mohanachari V, Reddy KS, Indiri K. 1984. Metabolic fate of ammonia in the rat after ethanol loading. Toxicol Lett 20:225-228.

*Moller D, Schieferdecker H. 1985. A relationship between agricultural NH_3 emissions and the atmospheric SO_2 content over industrial areas. Atmos Environ 19(5):695-700.

Monfort P, Kosenko E, Erceg S. 2002. Molecular mechanism of acute ammonia toxicity: role of NMDA receptors. Neurochem Int 41:95-102.

*Montague TJ, Macneil AR. 1980. Mass ammonia inhalation. Chest 77:496-498.

*Morgan SE. 1997. Ammonia pipeline rupture: Risk assessment to cattle. Vet Hum Toxicol 39(3):159-161.

*Mori S, Kaneko H, Mitsuma T, et al. 1998. Implications of gastric topical bioactive peptides in ammonia-induced acute gastric mucosal lesions in rats. Scand J Gastroenterol 33(4):386-393.

Morimoto Y, Ukida M, Tsuji T. 1988. Dynamic relationship between urea and glutamine synthesis in the mechanism of ammonia detoxication: A tracer study using $^{15}NH_4Cl$ in fulminant hepatic failure rats. Gastroenterol Jpn 23(5):538-545.

*Morris JC. 1978. Chemistry of aqueous chlorine in relation to water chlorination. In: Jolley RL, ed. Water chlorination: Environmental impact and health effects. Ann Arbor, MI: Ann Arbor Sci Pub, 21-36.

*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. Clin Pharmacokin 5:485-527.

*Mossberg SM, Ross G. 1967. Ammonia, movement in the small intestine: Preferential transport by the ileum. J Clin Invest 46(4):490-498.

Mouille B, Morel E, Robert V, et al. 1999. Metabolic capacity for L-citrulline synthesis from ammonia in rat isolated colonocytes. Biochim Biophys Acta 1427(3):401-407.

*Mulder JS, Van der Zalm HO. 1967. [Fatal case of ammonia poisoning.] T Soc Genecsk 45:458. (German)

*Munger JW. 1982. Chemistry of atmospheric precipitation in the North-Central United States. Atmos Environ 16(7):1633-1645.

*Muntwyler E, Iacobellis M, Griffin GE. 1956. Kidney glutaminase and carbonic anhydrase activities and renal electrolyte excretion in rats. Am J Physiol 184:83-90.

*Murakami M, Asagoe K, Dekigai H, et al. 1995. Products of neutrophil metabolism increase ammonia-induced gastric mucosal damage. Dig Dis Sci 40(2):268-273.

Murakami M, Saita H, Teramura S, et al. 1993. Gastric ammonia has a potent ulcerogenic action on the rat stomach. Gastroenterology 105(6):1710-1715.

Nadelhoffer K, Downs M, Fry B, et al. 1999. Controls on N retention and exports in a forested watershed. Environ Monit Assess 55(1):187-210.

Nagamine T, Saito S, Kaneko M, et al. 1995. Effect of biotin on ammonia intoxication in rats and mice. J Gastroenterol 30(3):351-355.

*Nagy L, Kusstatscher S, Hauschka PV, et al. 1996. Role of cysteine proteases and protease inhibitors in gastric mucosal damage induced by ethanol or ammonia in the rat. J Clin Invest 98(4):1047-1054.

Nakasaki K, Ohtaki A, Takano H. 2001. Effect of bulking agent on the reduction of NH3 emissions during thermophilic composting of night-soil sludge. Waste Manage Res 19(4):301-307.

Nakatsuka T, Fukikake M, Katoh M, et al. 1992. Amelioration of furosemide-induced fetal wavy ribs by co-administration of ammonium chloride in rats. Teratology 46(6):19B.

Nakatusa T, Fujikake N, Hasebe M, et al. 1993. Effects of sodium bicarbonate and ammonium chloride on the incidence of furosemide-induced fetal skeletal anomaly, wavy rib, in rats. Teratology 48(2):139-147.

Nakazawa S, Quastel JH. 1968. Inhibitory effects of ammonium ions and some amino acids on stimulated brain respiration and cerebral amino acid transport. Can J Biochem 46:543-548.

*NAS/NRC. 1989. Report of the oversight committee. In: Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press.

NASA. 1967. Means of determining the maximum allowable concentration of toxic products of natural human metabolism. Washington, DC: National Aeronautics and Space Administration.

*Nason GE, Pluth DJ, McGill WB. 1988. Volatilization and foliar recapture of ammonia following spring and fall application of nitrogen-15 urea to a douglas-fir ecosystem. Soil Sci Soc Am J 52:821-828.

NATICH. 1988. NATICH data base report on state, local and EPA air toxics activities. Research Triangle Park, NC: National Air Toxics Information Clearinghouse, U.S. Environmental Protection Agency.

Naumovski D, Pilovski G, Cibisev A, et al. 2001. Pulmonary injuries after exposure to irritative fumes of household cleaners. Toxicol Lett 123(Suppl 1):91-92.

Navazio F, Gerritsen T, Wright GJ. 1961. Relationship of ammonia intoxication to convulsions and coma in rats. J Neurochem 8:146-151.

NCI. 1975. In: Fraumeni JF, ed. Persons at high risk of cancer: An approach to cancer etiology and control. Bethesda, MD: National Cancer Institute.

Nemitz E, Sutton MA, Gut A, et al. 2000. Sources and sinks of ammonia within an oilseed rape canopy. Agric For Meteorol 105(4):385-404.

Nemitz E, Sutton MA, Schjoerring JK, et al. 2000. Resistance modelling of ammonia exchange over oilseed rape. Agric For Meteorol 105(4):405-425.

*Neumann R, Mehlhorn G, Buchholz I, et al. 1987. [Experimental studies of the effect of chronic exposure of suckling pigs to aerogenous toxic gas with ammonia of varying concentrations.] J Vet Med B34:241-253. (German)

New Jersey Department of Health. 1996a. Ammonium fluoride. Trenton, NJ: New Jersey Department of Health, Right to Know Program. www.state.nj.us/health/eoh/rtkweb/0099.pdf. April 1996

New Jersey Department of Health. 1996b. Ammonium carbamate. Trenton, NJ: New Jersey Department of Health, Right to Know Program. www.state.nj.us/health/eoh/rtkweb/0091.pdf. January 1996

Niden AH. 1968. Effects of ammonia inhalation on the terminal airways. Proc 11th Aspen Emphysema Conf 11:41-44.

Nieto R, Calder AG, Anderson SE, et al. 1996. Method for the determination of $^{15}NH_3$ enrichment in biological samples by gas chromatography electron impact ionization mass spectrometry. J Mass Spectrom 31(3):289-294.

*NIOSH. 1974. Occupational exposure to ammonia: Criteria for a recommended standard. Cincinnati, OH: National Institute for Occupational Safety and Health. NIOSH 74-136.

NIOSH. 1982. Background information on ammonia. Cincinnati, OH: U.S. National Institute for Occupational Safety and Health. PB82109984.

NIOSH. 1984. Ammonia Method 6701. NIOSH manual of analytical methods 1. Cincinnati, OH: National Institute for Occupational Safety and Health, 6701-1 to 6701-4.

NIOSH. 1985. NIOSH pocket guide to chemical hazards. Washington, DC: National Institute for Occupational Safety and Health.

*NIOSH. 1987. Health hazard evaluation report. Cincinnati, OH: National Institute for Occupational Safety and Health. PB87232948.

*NIOSH. 1988. National Occupational Exposure Survey (NOES). Cincinnati, OH: National Institute for Occupational Safety Health, 93.

*NIOSH. 1994. Ammonia. NIOSH manual of analytical methods (NMAM), August 15, Fourth edition, 1994. National Institute for Occupational Safety and Health.

*NIOSH. 1996. Ammonia by ICNIOSH manual of analytical methods (NMAM), May 15, Fourth edition, 1996. National Institute for Occupational Safety and Health.

*NIOSH. 2002a. Ammonia. NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/npg/npgd0028.html. June 06, 2004.

9. REFERENCES

*NIOSH. 2002b. Ammonia and ammonium chloride fume. NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health. wysiwyg://92/http://www.cdc.gov/niosh/npg/npg.html. May 02, 2002.

*Noda K, Chikamori K. 1976. Effect of ammonia via prepyriform cortex on regulation of food intake in the rat. Am J Physiol 231:1263-1266.

*NOES. 1989. Ammonia. National Occupational Exposure Survey. March 29, 1989, 19.

Norenberg MD. 1996. Astrocytic-ammonia interactions in hepatic encephalopathy. Semin Liver Dis 16(3):245-253.

*NRC. 1979. Transport and distribution of ammonia and the effect of pH. In: National Research Council, ed. Ammonia. Baltimore, MD: University Park Press.

*NRC. 1993. Pesticides in the diets of infants and children. Washington, DC: National Academy Press, National Research Council.

*NSF. 1999. Interim report: Environmental science and engineering for the 21st century. The role of the National Science Foundation. Arlington, VA: National Science Foundation. NSB 99-133.

O'Connor JE, Costell M, Grisolía S. 1984. Prevention if ammonia toxicity by L-carnitine: Metabolic changes in the brain. Neurochem Res 9(4):563-570.

*O'Connor JE, Costell M, Grisolía S. 1987. The potentiation of ammonia toxicity by sodium benzoate is prevented by L-Carnitine. Biochem Biophys Res Commun 145(2):817-824.

O'Connor JE, Costell M, Grisolía S. 1989. Carbamyl glutamate prevents the potentiation of ammonia toxicity by sodium benzoate. Eur J Pediatr 148(6):540-542.

*O'Connor JE, Guerri C, Grisolía S. 1982. Protective effect of ethanol on acute ammonia intoxication in mice. Biochem Biophys Res Commun 104(2):410-415.

*O'Deen WA, Porter LK. 1986. Continuous flow system for collecting volatile ammonia and amines from senescing winter wheat. Agron J 78:746-749.

OHM-TADS. 1988. Oil and Hazardous Materials Technical Assistance Data System. Washington, DC: Environmental Protection Agency, National Institute of Health.

Ohtsuka Y, Griffith OW. 1991. L-carnitine protection in ammonia intoxication. Effect of aminocarnitine on carnitine-dependent metabolism and acute ammonia toxicity. Biochem Pharmacol 41(12):1957-1961.

Okita M, Watanabe A, Tsuji T. 1988. Effect of branched-chain amino acid on ^{15}N incorporation into liver and skeletal muscle proteins following [^{15}N]-ammonium chloride administration to carbon tetrachloride-intoxicated rats. J Nutr Sci Vitaminol 34(1):85-96.

*Olavarria JS, Artacho E, Sánchez F, et al. 1986. Synergistic effect of ammonia and potassium ions on pyruvate kinase from Ehrlich ascites tumor cells. Enzyme 35:34-41.

9. REFERENCES

*Olivier JGJ, Bouwman AF, Van der Hoek KW, et al. 1998. Global air emission inventories for anthropogenic sources of NO_X, NH_3 and N_2O in 1990. Environ Pollut 102:135-148.

Onay TT, Pohland FG. 2001. Nitrogen and sulfate attenuation in simulated landfill bioreactors. Water Sci Technol 44(2-3):367-372.

OSHA. 1985. Permissible exposure limits (Table Z-1). Occupational Safety and Health Administration. Code of Federal Regulations. CFR 29(1910.1000):655-659.

*OSHA. 1998. U. S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000.

*OSHA. 2001. Occupations in agriculture particularly hazardous for the employment of children below the age of 16. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 570.71. http://frwebgate.access.gpo.gov/. May 02, 2002.

*OSHA. 2002a. Air contaminants. Occupational safety and health standards for shipyard employment. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000. http://www.osha.gov/. May 02, 2002.

*OSHA. 2002b. Blasting and the use of explosives. Safety and health regulations for construction. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.914(e). http://www.osha.gov/. May 02, 2002.

*OSHA. 2002c. Gases, vapors, fumes, dusts, and mists. Safety and health regulations for construction. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55. Appendix A. http://www.osha.gov/. May 02, 2002.

*OSHA. 2002d. Limits for air contaminants. Occupational safety and health standards. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000. Table Z-1. http://www.osha.gov/. May 02, 2002.

*OSHA. 2002e. List of highly hazardous chemicals, toxics and reactives. Occupational safety and health standards. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.119. Appendix A. http://www.osha.gov/. May 02, 2002.

*OSHA. 2002f. List of highly hazardous chemicals, toxics and reactives. Safety and health regulations for construction. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.64. http://www.osha.gov/. May 02, 2002.

*OSHA. 2002g. Storage and handling of anhydrous ammonia. Occupational safety and health standards. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.111. http://www.osha.gov/. May 02, 2002.

Paik WK, Lawson D, Kim S. 1975. Effect of endocrine glands on the protection of rat from ammonia intoxication. Life Sci 15:1189-1196.

Pal T, Pal A, Miller GH, et al. 1992. Passive dosimeter for monitoring ammonia vapor. Anal Chim Acta 263(1-2):175-178.

Paramasivam S, Alva AK, Fares A. 2000. Transformation and transport of nitrogen forms in a sandy entisol following a heavy loading of ammonium nitrate solution: Field measurements and model simulations. J Soil Contam 9(1):65-86.

*Parris N. 1984. An improved fluorometric method for the determination of ammonia and volatile amines in meat tissue by high-performance liquid chromatography. J Agric Food Chem 32:829-831.

*Parris N, Foglia TA. 1983. Simplified alcoholic extraction procedure for ammonia in meat tissue. J Agric Food Chem 31:887-889.

*Parton WJ, Morgan JA, Altenhofen JM, et al. 1988. Ammonia volatilization from spring wheat plants. Agron J 80:419-425.

Pascuzzi TA, Storrow AB. 1998. Mass casualties from acute inhalation of chloramine gas. Mil Med 163(2):102-104.

Paul V. 2003. Inhibition of acute hyperammonemia-induced convulsions by systemically administered gamma aminobutyric acid in rats. Pharmacol Biochem Behav 74:523-528.

*Payne WJ. 1981. Denitrification. New York, NY: John Wiley and Sons.

Perry GF. 1995. Occupational medicine forum. J Occup Environ Med 37(10):1187-1188.

Pinson DM, Schoeb TR, Lin SL, et al. 1988. Promotion of mycoplasma-pulmonis growth in rat tracheal organ cultures by ammonium chloride. Lab Anim Sci 38(2):143-147.

*Pitts RF. 1971. The role of ammonia production and excretion in regulation of acid-base balance. N Engl J Med 284:32-38.

*Plerson WR, Brachaczek WW. 1983. Emissions of ammonia and amines from vehicles on the road. Environ Sci Technol 17:757-760.

*Pranitis DM, Meyerhoff ME. 1987. Continuous monitoring of ambient ammonia with a membrane-electrode-based detector. Anal Chem 59:2345-2350.

*Price SK, Hughes JE, Morrison SC, et al. 1983. Fatal ammonia inhalation-A case report with autopsy findings. S Afr Med J 64:952-955.

Prokop'eva AS, Yushkov GG. 1975. [Materials for a toxicological characteristic of the repeated effects of ammonia on the organs of animals after brief exposure.] Gig Tr Prof Zabol 9:54-55. (Russian)

*Prokop'eva AS, Yushkov GG, Ubasheev IO. 1973. [Materials for a toxicologial characteristic of the one-time effect of ammonia on the organisms of animals after brief exposures.] Gig Tr Prof Zabol 6:56-57. (Russian)

*Prudhomme JC, Shusterman DJ, Blanc PD. 1998. Acute-onset persistent olfactory deficit resulting from multiple overexposures to ammonia vapor at work. J Am Board Fam Pract 11(1):66-69.

Raabe W. 1989. Neurophysiology of ammonia intoxication. In: Butterworth RF, Pomier Layrargues G, eds. Hepatic encephalopathy: Pathophysiology and treatment. Clifton, NJ: Humana Press, 49-77.

9. REFERENCES

*Raabe W. 1992. Ammonium ions abolish excitatory synaptic transmission between cerebellar neurons in primary dissociated tissue culture. J Neurophysiol 68:93-99.

Raabe W, Gumnit RJ. 1975. Inhibition of cat motor cortex by ammonia. J Neurophysiol 38:347-355.

Raabe W, Lin S. 1984. Ammonia, postsynaptic inhibition and CNS-energy state. Brain Res 303:67-76.

*Rabkin R, Palathumpat M, Tsao T. 1993. Ammonium chloride alters renal tubular cell growth and protein turnover. Lab Invest 68(4):427-438.

*Rajagopal R. 1978. Impact of land use on ground water quality in the Grand Traverse Bay Region of Michigan. J Environ Qual 7(1):93-98.

Rama Rao KV, Jayakumar AR, Norenberg MD. 2003. Ammonia neurotoxicity: Role of the mitochondrial permeability transition. Metab Brain Dis 18(2):113-127.

*Rapsomanikis S, Wake M, Kitto AMN, et al. 1988. Analysis of atmospheric ammonia and particulate ammonium by a sensitive fluorescence method. Environ Sci Technol 22:948-952.

*Reynolds CM, Wolf DC. 1988. Effects of field methods and soil cover on estimating ammonia loss from nitrogen-15-urea. Soil Sci Soc Am J 52:706-712.

*Reynolds SJ, Donham KJ, Whitten P, et al. 1996. Longitudinal evaluation of dose-response relationships for environmental exposures and pulmonary function in swine production workers. Am J Ind Med 29(1):33-40.

*Richard D, Bouley G, Boudene C. 1978a. [Effects of continuous inhalation of ammonia in the rat and mouse.] Bull Eur Physiopathol Respir 14:573-582. (French)

*Richard D, Jouany JM, Boudene C. 1978b. [Acute toxicity of ammonia gas in the rabbit by inhalation.] C R Acad Hebd Seances Acad Sci Ser D 287:375-378. (French)

*Richards P, Brown CL, Houghton BJ, et al. 1975. The incorporation of ammonia nitrogen into albumin in man: the effects of diet, uremia and growth hormone. Clin Nephrol 3(5):172-179.

*Robin ED, Travis DM, Bromberg PA, et al. 1959. Ammonia excretion by mammalian lung. Science 129:270-271.

*Rogers HH, Anjea VP. 1980. Uptake of atmospheric ammonia by selected plant species. Environ Exp Bot 20:251-257.

Ros M, Gantar A. 1998. Possibilities of reduction of recipient loading of tannery wastewater in Slovenia. Water Sci Technol 37(8):145-152.

*Rosenbaum AM, Walner DL, Dunham ME, et al. 1998. Ammonia capsule ingestion causing upper aerodigestive tract injury. Otolaryngol Head Neck Surg 119(6):678-680.

*Rosenfeld M. 1932. [Experimental modification of mitosis by ammonia.] Arch Exp Zellforsch Besonders Gewebezvecht 14:1-13. (German)

9. REFERENCES

*Rosswall T. 1981. The biogeochemical nitrogen cycle. In: Likens GE, ed. Some perspectives of the major biogeochemical cycles. New York, NY: John Wiley and Sons, 25-49.

Rostron WM, Stuckey DC, Young AA. 2001. Nitrification of high strength ammonia wastewaters: comparative study of immobilisation media. Water Res 35(5):1169-1178.

*Roy GS, Poricha RR. 1982. Ammonia nitrogen in fertiliser industry effluents - present status. Proc No R&D (Fert Assoc India)3:126-132.

*RTECS. 1988. Registry of toxic effects of chemical substances. Cincinnati, OH: National Institute for Occupational Safety and Health.

Rupp W, Sauer R, Hinz A. 1995. CO_2-laser sensor system for ammonia. Proc SPIE Int Soc Opt Eng 2506:162-166.

*Russell AG, McCue KF, Cass GR. 1988. Mathematical modeling of the formation of nitrogen-containing air pollutants. 1. Evaluation of an Eulerian photochemical model. Environ Sci Technol 22:263-271.

*Ryan JA, Keeney DR. 1975. Ammonia volatilization from surface-applied wastewater sludge. J Water Pollut Control Fed 47:386-393.

*Ryden JC, Whitehead DC, Lockyer DR, et al. 1987. Ammonia emission from grassland and livestock production systems in the UK. Environ Pollut 48:173-184.

Ryer-Powder JE. 1991. Health effects of ammonia. Plant/Oper Prog 10(4):228-232.

Sadasivudu B, Murthy RK. 1978. Effects of ammonia on monoamine oxidase and enzymes of GABA metabolism in mouse brain. Arch Int Physiol Biochim 86:67-82.

Sadasivudu B, Murthy CRK, Rao GN, et al. 1983. Studies on acetylcholinesterase and gamma-glutamyltranspeptides in mouse brain in ammonia toxicity. J Neurosci Res 9:127-134.

Sadasivudu B, Rao TI, Radhakrishna C. 1977. Acute metabolic effects of ammonia in mouse brain. Neurochem Res 2:639-655.

Sadasivudu B, Rao TI, Radhakrishna M. 1979. Chronic metabolic effects of ammonia in mouse brain. Arch Int Physiol Biochim 87:871-885.

*Salvatore F, Bocchinti V, Cimino F. 1963. Ammonia intoxication and its effects on brain ammonia levels. Biochem Pharmacol 12:1-6.

Saran T, Hilgier W, Kocki T, et al. 1998. Acute ammonia treatment in vitro and in vivo inhibits the synthesis of a neuroprotectant kynurenic acid in rat cerebral cortical slices. Brain Res 787(2):348-350.

Sato A, Gonmori K, Yoshioka N. 1999. A case of fatal intoxication with ammonium sulfate and a toxicological study using rabbits. Forensic Sci Int 101(2):141-149.

*Saul RL, Archer MC. 1984. Oxidation of ammonia and hydroxylamine to nitrate in the rat and in vitro. Carcinogenesis 5(1):77-81.

9. REFERENCES

*Sax NI, Lewis RJ, eds. 1987. Hawley's condensed chemical dictionary. New York, NY: Van Nostrand Reinhold, 1288.

*Schaerdel AD, White WJ, Lang CM, et al. 1983. Localized and systemic effects of environmental ammonia in rats. Lab Anim Sci 33(1):40-45.

Schenker S, Mendelson JH. 1964. Cerebral adenosine triphosphate in rats with ammonia-induced coma. Am J Physiol 206:1173-1176.

Schenker S, Warren KS. 1962. Effect of temperature variation on toxicity and metabolism of ammonia in mice. J Lab Clin Med 60(2):291-301.

Schenker S, McCandless DW, Brophy E, et al. 1967. Studies on the intracerebral toxicity of ammonia. J Clin Invest 46:838-848.

*Schubiger G, Bachmann C, Barben P, et al. 1991. N-acetylglutamate synthetase deficiency: diagnosis, management and follow-up of a rare disorder of ammonia detoxication. Eur J Pediatr 150(5):353-356.

*Scuurkes JAAR, Maenen MMJ, Roelofs JGM. 1988. Chemical characteristics of precipitation in NH_3-affected areas. Atmos Environ 22(8):1689-1698.

*Seegal BC. 1927. Chronic acidosis in rabbits and in dogs. Arch Intern Med 39:550-563.

Seiler N. 1993. Is ammonia a pathogenetic factor in Alzheimer's disease? Neurochem Res 18(3):235-245.

*Seiler N. 2002. Review: Ammonia and Alzheimer's disease. Neurochem Int 41:189-207.

Seiler N, Sarhan S, Knoedgen B, et al. 1993. Enhanced endogenous ornithine concentrations protect against tonic seizures and coma in acute ammona intoxication. Pharmacol Toxicol 72(2):116-123.

*Seitzinger SP. 1987. Nitrogen biogeochemistry in an unpolluted estuary: The importance of benthic denitrification. Mar Ecol Prog Ser 41:177-186.

*Sekizawa SI, Tsubone H. 1994. Nasal receptors responding to noxious chemical irritants. Respir Physiol 96(1):37-48.

Semama DS, Huet F, Gouyon JB, et al. 1995. Use of peritoneal dialysis, continuous arteriovenous hemofiltration, and continuous arteriovenous hemodiafiltration for removal of ammonium chloride and glutamine in rabbits. J Pediatr 126:742-746.

Seo Y, Murakami M. 1991. Monitoring of intracellular immonium in perfused rat salivary gland by nitrogen-14 nuclear magnetic resonance spectroscopy. Proc R Soc London, Ser B 244(1311):191-196.

Sharara FI, Seifer DB, Flaws JA. 1998. Environmental toxicants and female reproduction. Fertil Steril 70(4):613-622.

Shibata M-A, Tamano S, Kurata Y, et al. 1989. Participation of urinary sodium potassium and L-ascorbic acid in the proliferative response of the bladder epithelium after the oral administration of various salts and-or ascorbic acid to rats. Food Chem Toxicol 27(6):403-413.

9. REFERENCES

*Shimkin MB, de Lorimier AA, Mitchell JR, et al. 1954. Appearance of carcinoma following single exposure to a refrigeration ammonia-oil mixture. Arch Ind Hyg Occup Med 9:186-193.

Shitara Y, Kato Y, Sugiyama Y. 1998. Effect of brefeldin A and lysosomotropic reagents on intracellular trafficking of epidermal growth factor and transferrin in Madin-Darby canine kidney epithelial cells. J Controlled Release 55:35-43.

*Sine C, ed 1987. Farm chemicals handbook. Willoughby, OH: Meister Publishing Co., B16-B19.

Silver SD, McGrath FP. 1948. A comparison of acute toxicities of ethylene imine and ammonia to mice. J Ind Hyg Toxicol 30:7-9.

*Silverman L, Whittenberger JL, Muller J. 1949. Physiological response of man to ammonia in low concentrations. J Ind Hyg Toxicol 31:74-78.

*Sjöblom E, Hojer J, Kulling PE, et al. 1999. A placebo-controlled experimental study of steroid inhalation therpy in ammonia-induced lung injury. J Toxicol Clin Toxicol 37(1):59-67.

*Sloan CH, Morie GP. 1974. Determination of ammonia in tobacco and tobacco smoke with an ammonia electrode. Anal Chim Acta 69:243-247.

*Slot GMJ. 1938. Electrocardiograms in 80 cases of angina of effort. Lancet 2:1356-1357.

Smith LG, Busch RH, Buschbom RL, et al. 1989. Effects of sulfur dioxide or ammonium sulfate exposure, alone or combined, for 4 or 8 months on normal and elastase-impaired rats. Environ Res 49(1):60-78.

*Snodgrass WJ, Ng PS. 1985. Biochemical models for the hypolimnetic oxygen depletion in lakes impacted by wastewater discharges 1. Alternative models. Arch Hydrobiol Suppl 72:81-109.

Soar JB, Buttery PJ, Lewis D. 1973. Ammonia toxicity in sheep. Proc Nutr Soc 32:77A-78A.

*Sobel RA, DeArmond SJ, Forno LS, et al. 1981. Glial fibrillary acidic protein in hepatic encephalopathy. J Neuropathol Exp Neurol 40:625-632.

*Sobonya R. 1977. Fatal anhydrous ammonia inhalation. Hum Pathol 8:293-299.

*Socolow RH. 1999. Nitrogen management and the future of food: Lessons from the management of energy and carbon. Proc Natl Acad Sci USA 96:6001-6008.

Sorial GA, Smith FL, Suidan MT, et al. 2001. Removal of ammonia from contaminated air by trickle bed air biofilters. J Air Waste Manage Assoc 51(5):756-765.

Sotiropoulos G, Kilaghbian T, Dougherty W, et al. 1998. Cold injury from pressurized liquid ammonia: a report of two cases. J Emerg Med 16(3):409-412.

Spengler JD, Koutrakis P, Dockery DW, et al. 1996. Health effects of acid aerosols on North American children: Air pollution exposures. Environ Health Perspect 104(5):492-499.

*Sprenger U, Bachmann K. 1987. Determination of ammonium in aerosols, cloud and rain water, and of gaseous ammonia in the troposphere. Fresenius Z Anal Chem 327:16.

9. REFERENCES

*SRI. 1988. Directory of chemical producers USA. Menlo Park, CA: SRI International, 457-465.

*SRI. 2000. Directory of chemical producers USA. Menlo Park, CA: SRI International, 457-463.

*Stabenau JR, Warren KS, Rall DP. 1958. The role of pH gradient in the distribution of ammonia between blood and cerebro-spinal fluid, brain and muscle. J Clin Invest 38:373-383.

Steppuhn H, Coxworth E, Kernan JA, et al. 1994. Response of *Kochia scoparia* to nitrogen fertilization on a saline soil. Can J Soil Sci 74(3):267-275.

*Stombaugh DP, Teague HS, Roller WL. 1969. Effects of atmospheric ammonia on the pig. J Anim Sci 28:844-847.

*Strogies M, Kallweit D. 1996. Nitrogen emissions in Germany and potential for their reduction. In: Sutton MA, Lee DS, Dollard GJ, et al., eds. Atmospheric ammonia: Emission deposition and environmental impacts: Poster proceedings. Midlothian, UK: Institute of Terrestrial Ecology, 53-56.

*Stroud S. 1981. Ammonia inhalation-A case report. Crit Care Nurse 1:23-26.

Stumpe JM, Vlek PLG. 1991. Acidification induced by different nitrogen sources in columns of selected tropical soils. Soil Sci Soc Am J 55(1):145-151.

*Stupfel M, Romary F, Magnier M, et al. 1971. [Comparative acute toxicity of several atmospheric pollutants, in male and female mice: Automobile exhaust gases, nitrogen oxides, sulfur dioxide, ozone, ammonia and carbon dioxide.] C R Seances Soc Biol Fil 19:1869-1872. (French)

*Suárez I, Bodega G, Arilla E, et al. 1992. Different response of astrocytes and Bergmann glial cells to portacaval shunt. An immunohistochemical study in the rat cerebellum. Glia 6:172-179.

Suárez I, Bodega G, Fernandez B. 2002. Glutamine synthetase in brain: effect of ammonia. Neurochem Int 41:123-142.

*Suh HH, Spengler JD, Koutrakis P. 1992. Personal exposures to acid aerosols and ammonia. Environ Sci Technol 26(12):2507-2517.

*Summerskill WHJ, Wolpert E. 1978. Ammonia metabolism in the gut. Am J Clin Nutr 23:633-639.

*Sunesson AL, Gullberg J, Blomquist G. 2001. Airborne chemical compounds on dairy farms. J Environ Monitor 3(2):210-216.

Suzuki H, Yanaka A, Nakahara A, et al. 2000. The mechanism of gastric mucosal apoptosis induced by ammonia. Gastroenterology 118(Suppl 2):AGA A734.

Swotinsky RB, Chase KH. 1990. Health effects of exposure to ammonia: Scant information. Am J Ind Med 17(4):515-521.

Takagaki G, Berl S, Clarke DD, et al. 1961. Glutamic acid metabolism in brain and liver during infusion with ammonia labelled with nitrogen-15. Nature 189:326.

9. REFERENCES

*Takahashi H, Koehler RC, Brusilow SW, et al. 1991. Inhibition of brain glutamine accumulation prevents cerebral edema in hyperammonemic rats. Am J Physiol 261:H825-H829.

*Takeuchi K, Ohuchi T, Harada H, et al. 1995. Irritant and protective action of urea-urease ammonia in rat gastric mucosa. Dig Dis Sci 40(2):274-281.

Tannenbaum SR, Young VR. 1980. Endogenous nitrite formation in man. J Environ Pathol Toxicol 3:357-368.

*Tanner RL. 1982. An ambient experimental study of phase equilibrium in the atmospheric system: aersol H^+, NH^+_4, SO^{2-}_4, NO^-_3–$NH_{3(g)}$, $HNO_{3(g)}$. Atmos Environ 16(12):2935-2942.

*Taplin GV, Chopra S, Yanda RL, et al. 1976. Radionuclidic lung-imaging procedures in the assessment of injury due to ammonia inhalation. Chest 69:582-586.

*Targowski SP, Klucinski W, Babiker S, et al. 1984. Effect of ammonia on in vivo and in vitro immune response. Infect Immun 43(1):289-293.

Tarr MA, Wang W, Bianchi TS, et al. 2001. Mechanisms of ammonia and amino acid photoproduction from aquatic humic and colloidal matter. Water Res 35(15):3688-3696.

*Tepper A, Constock GW, Levine M. 1991. A longitudinal study of pulmonary function in fire fighters. Am J Ind Med 20(3):307-316.

*Tepper JS, Weiss B, Wood RW. 1985. Alterations in behavior produced by inhaled ozone or ammonia. Fundam Appl Toxicol 5:1110-1118.

Thomas RC. 1974. Intracellular pH of snail neurons measured with a new pH-sensitive glass micro-electrode. J Physiol 238:159-180.

Thomson CJ, Marschner H, Roemheld V. 1993. Effect of nitrogen fertilizer form on pH of the bulk soil and rhizosphere and on the growth, phosphorus, and micronutrient uptake of bean. J Plant Nutr 16(3):493-506.

Thornton FC, Bock BR, Tyler DD. 1996. Soil emissions of nitric oxide and nitrous oxide from injected anhydrous ammonium and urea. J Environ Qual 25:1378-1384.

*Tian G, Cai Z, Cao J, et al. 2001. Factors affecting ammonia volatilisation from a rice-wheat rotation system. Chemosphere 42(2):123-129.

*Tietz NW, ed. 1970. Fundamentals of clinical chemistry. Philadelphia, PA: W.B. Saunders Company.

Tonkiss J, Trzcinska M, Galler JR, et al. 1998. Prenatal malnutrition-induced changes in blood pressure: dissociation of stress and nonstress responses using radiotelemetry. Hypertension 32(1):108-114.

Topping DC, Visek WJ. 1976. Nitrogen intake and tumorigenesis in rats injected with 1,2-dimethylhydrazine. J Nutr 106:1583-1590.

Torda C. 1952. Ammonium ion content and electrical activity of the brain during the preconvulsive and convulsive phases induced by various convulsants. J Pharmacol Exp Ther 197:197-203.

Torres VE, Keith DS, Offord KP, et al. 1994. Renal ammonia in autosomal dominant polycystic kidney disease. Kidney Int 45(6):1745-1753.

*Toth B. 1972. Hydrazine, methylhydrazine and methylhydrazine sulfate carcinogenesis swiss mice. Failure of ammonium hydroxide to interfere in the development of tumors. Int J Cancer 9:109-118.

*TRI 01. 2003. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*Tsibulski V, Yatsenko-Khmelevskaya M, Milyaev V, et al. 1996. Ammonia emissions in Russia. In: Sutton MA, Lee DS, Dollard GJ, et al., eds. Atmospheric ammonia: Emission deposition and environmental impacts: Poster proceedings. Midlothian, UK: Institute of Terrestrial Ecology, 50-52.

Tsujii M, Kawano S, Tsuji S, et al. 1992a. Ammonia: A possible promotor in *Helicobacter pylori*-related gastric carcinogenesis. Cancer Lett 65(1):15-18.

*Tsujii M, Kawano S, Tsuji S, et al. 1992b. Mechanism of gastric mucosal damage induced by ammonia. Gastroenterology 102(6):1881-1888.

*Tsujii M, Kawano S, Tsuji S, et al. 1993. Cell kinetics of mucosal atrophy in rat stomach induced by long-term administration of ammonia. Gastroenterology 104(3):796-801.

*Tsujii M, Kawano S, Tsuji S, et al. 1995. Mechanism for ammonia-induced promotion of gastric carcinogenesis in rats. Carcinogenesis 16(3):563-566.

Turtureanu M. 1994. Ammonia production. In: Hodge CA, Popovici NN, eds. Pollution control in fertilizer production. New York, NY: Marcel Dekker, Inc, 35-50.

*Tuskes PM, Tilton MA, Graff RM. 1988. Ammonia exposures of blue-line printers in Houston, Texas. Appl Ind Hyg 3:155-157.

*Tyor MP, Owen EE, Berry JN, et al. 1960. The relative role of extremity, liver, and kidney as ammonia receivers and donors in patients with liver disease. Gastroenterology 39:420-424.

*Urbain B, Gustin P, Prouvost JF, et al. 1994. Quantitative assessment of aerial ammonia toxicity to the nasal mucosa by use of the nasal lavage method in pigs. Am J Vet Res 55(9):1335-1340.

*U.S. Army Corps of Engineers. 1980. Wastewater treatment in cold regions by overland flow. Washington, DC: U.S. Army Corps of Engineers.

*USC. 2002a. Assurances of availability of adequate supplies of chemicals necessary for treatment of water. United States Code. 42 USC 300j. http://www4.law.cornell.edu/uscode/42/300j.html. May 02, 2002.

*USC. 2002b. Definitions and special rules. United States Code. 26 USC 4662. http://www4.law.cornell.edu/uscode/26/4662.html. May 02, 2002.

*USC. 2002c. Definitions and special rules. United States Code. 26 USC 4672. http://www4.law.cornell.edu/uscode/26/4672.html. May 02, 2002.

9. REFERENCES

*USC. 2002d. Imposition of tax. United States Code. 26 USC 4661. http://www4.law.cornell.edu/uscode/26/4661.html. May 02, 2002.

*Utell MJ, Mariglio JA, Morrow PE, et al. 1989. Effects of inhaled acid aerosols on respiratory function: The role of endogenous ammonia. J Aerosol Med 2:141-147.

*Uzvolgyi E, Bojan F. 1980. Possible in vivo formation of a carcinogenic substance from diethyl pyrocarbonate and ammonia. J Cancer Res Clin Oncol 97:205-207.

*Uzvolgyi E, Bojan F. 1985. In vivo formation of a carcinogenic substance from diethyl pyrocarbonate in the presence of ammonia. Arch Toxicol Suppl 8:490-493.

Valdes-Solis T, Marban G, Fuertes AB. 2001. Low-temperature SCR of NO_x with NH_3 over carbon-ceramic cellular monolith-supported manganese oxides. Catal Today 69(1-4):259-264.

van Dongen U, Jetten MSM, van Loosdrecht MCM. 2001. The SHARON-Anammox process for treatment of ammonium rich wastewater. Water Sci Technol 44(1):153-160.

*Van Hoesen SD, Dreibelbis WG. 1984. University of Minnesota-Duluth low-BTU gasifier workplace environment. In: Cowser KE, Jacobs VE, eds. Proceedings of the 5th life science symposium: Synthetic fossil fuel technologies. Boston, MA: Butterworth, 149-184.

*Van Slyke DD, Phillips RA, Hamilton PB, et al. 1943. Glutamine as source material of urinary ammonia. J Biol Chem 150:481-482.

*Verberk MM. 1977. Effects of ammonia in volunteers. Int Arch Occup Environ Health 39:73-81.

*Verschueren K. 1983. Handbook of environmental data on organic chemicals. 2nd ed. New York, NY: Van Nostrand Reinhold Company, 194.

Vernot EH, MacEwen JD, Haun CC, et al. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol Appl Pharmacol 42:417-423.

Visek WJ. 1984. Ammonia: Its effects on biological systems, metabolic hormones, and reproduction. J Dairy Sci 67(3):481-498.

*Visek WJ, Kolodny GM, Gross PR. 1972. Ammonia effects in cultures of normal and transformed 3T3 cells. J Cell Physiol 1972:373-381.

*Vitti TG, Vukmirovich R, Gaebler OH. 1964. Utilization of ammonia nitrogen, administered by intragastric, intraperitonal, and subcutaneous routes: Effects of growth hormone. Arch Biochem Biophys 106:475-482.

*Vogelzang PFJ, van der Gulden JWJ, Folgering H, et al. 2000. Longitudinal changes in bronchial responsiveness associated with swine confinement dust exposure. Chest 117(5):1488-1495.

*Vogelzang PFJ, van der Gulden JWJ, Preller L, et al. 1997. Bronchial hyperresponsiveness and exposure in pig farmers. Int Arch Occup Environ Health 70(5):327-333.

*Voisin C, Guerrin H, Furon D, et al. 1970. Sequelles fonctionnelles respiratoires des intoxications par l'ammoniac (a propos de 8 obserbations). Le Poumon et le Coeur 26:1079-1095.

9. REFERENCES

Walker CO, Schienker S. 1970. Pathogenesis of hepatic encephalopathy- with special reference to the role of ammonia. Am J Clin Nutr 23(5):619-632.

*Walton M. 1973. Industrial ammonia gassing. Br J Ind Med 30:78-86.

*Wands RC. 1981. Alkaline materials. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology, Vol. II, 4th ed. New York, NY: John Wiley & Sons, Inc., 3045-3069.

*Ward K, Costello GP, Murray B. 1983. Acute and long-term pulmonary sequelae of acute ammonia inhalation. Ir Med J 76(6):279-281.

Warland JS, Dias GM, Thurtell GW. 2001. A tunable diode laser system for ammonia flux measurements over multiple plots. Environ Pollut 114(2):215-221.

Warren KS. 1958. The differential toxicity of ammonia salts. J Clin Invest 37:497-501.

Warren KS, Nathan DG. 1958. The passage of ammonia across the blood-brian-barrier and its relation to blood pH. J Clin Invest 37:1724-1728.

*Warren KS, Schenker S. 1964. Effect of inhibitor glutamine synthesis (methionine sulfoximine) on ammonia toxicity and metabolism. J Lab Clin Med 64(3):442-449.

Wason S, Stephan M, Breide C. 1990. Ingestion of aromatic ammonia smelling salts capsules. Am J Dis Child 144(2):139-140.

Weast RC, Astle MJ, Beyer WH, eds. 1983. CRC handbook of chemistry and physics. Boca Raton, FL: CRC Press, Inc., B-69, D-163, D-222-223.

*Weast RC, Astle MJ, Beyer WH, eds. 1988. CRC Handbook of chemistry and physics. Boca Raton, Florida: CRC Press, Inc.

*Weatherby JH. 1952. Chronic toxicity of ammonia fumes by inhalation. Proc Soc Exp Biol Med 81:300-301.

*Weber FL, Veach GL. 1979. The importance of the small intestine in gut ammonium production in the fasting dog. Gastroenterology 77:235-240.

*Weedon FR, Hartzell A, Setterstrom C. 1940. Toxicity of ammonia, chlorine, hydrogen cyanide, hydrogen sulphide, and sulphur dioxide gases. V. Animals. Contrib Boyce Thompson Inst 11:365-385.

*Weir DC, Robertson AS, Jones S, et al. 1989. Occupational asthma due to soft corrosive soldering fluxes containing zinc chloride and ammonium chloride. Thorax 44(3):220-223.

*Weiser JR, Mackenroth T. 1989. Acute inhalatory mass ammonia intoxication with fatal course. Exp Pathol 37(1-4):291-295.

Weisskopf MG, Drew JM, Hanrahan LM, et al. 2003. Hazardous ammonia releases: Public health consequences and risk factors for evacuation and injury, United States, 1993-1998. J Occup Environ Med 45:197-204.

9. REFERENCES

*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Pediatr 32:10-18.

Westra HG, van Doorn JE, Tigchelaar RG. 2001. A method for the determination of volatile ammonia in air, using a nitrogen-cooled trap and fluorometric detection. Anal Biochem 296(2):225-231.

*White ES. 1971. A case of near fatal ammonia gas poisoning. J Occup Med 13:543-550.

*WHO. 1986. Ammonia. Environmental Health Criteria. Vol. 54. Geneva, Switzerland: World Health Organization.

*WHO. 2002. Guidelines for drinking water. World Health Organization. http://www.who.int./water_sanitiation_health/GDWQ/Chemicals/ammonsum.htm. May 02, 2002.

*Wibbenmeyer LA, Morgan LJ, Robinson BK, et al. 1999. Our chemical burn experience: Exposing the dangers of anhydrous ammonia. J Burn Care Rehab 20(3):226-231.

*Wicherski B. 2000. Groundwater quality investigation and wellhead protection study. City of Fruitland, Idaho. Boise, Idaho: Idaho Department of Environmental Quality. Technical Services Division.

Wieslander G, Norback D, Edling C. 1994. Occupational exposure to water based paint and symptoms from the skin and eyes. Occup Environ Med 51(3):181-186.

*Wilkin DC, Flemal RC. 1980. Feasibility of water quality improvemnet in three Illinois rivers. J Water Pollut Control Fed 52(2):293-298.

Williams PI, Gallagher MW, Choularton TW, et al. 2000. Aerosol development and interaction in an urban plume. Aerosol Sci Technol 32(2):120-126.

Wilson RP, Muhrer ME, Bloomfield RA. 1968. Comparative ammonia toxicity. Comp Biochem Physiol 25:295-301.

*Windholz M, Budavari S, Blumetti RF, et al., eds. 1983. The Merck index, 10th ed. Rahway, NJ: Merck & Co., Inc.

*Withers J, Ten Berge W, Gordon J, et al. 1986. The lethal toxicity of ammonia: A report to the MHAP. Northwestern Branch Papers 1986 1:6.1-6.27.

Wood CW, Marshall SB, Cabera ML. 2000. Improved method for field-scale measurement of ammonia volatization. Commun Soil Sci Plant Anal 31(5-6):581-590.

Wood RW. 1979. Behavioral evaluation of sensory irritation evoked by ammonia. Toxicol Appl Pharmacol 50:157-162.

Worcel A, Erecinska M. 1962. Mechanism of inhibitory action of ammonia on the respiration of rat-liver mithochondria. Biochim Biophys Acta 65:27-33.

Wrenn C. 2000. Real-time measurement of ammonia gas. Occup Health Safe 69(12):64-67.

Wu G, Pond WG, Ott T, et al. 1998. Maternal dietary protein deficiency decreases amino acid concentrations in fetal plasma and allantoic fluid of pigs. J Nutr 128(5):894-902.

Wysmyk U, Oka SS, Saransaari P, et al. 1994. Long-term treatment with ammonia effects the content and release of taurine in cultured cerebellar astrocytes and granule neurons. Neurochem Int 24(4):317-322.

*Yadav JS, Kaushik VK. 1997. Genotoxic effect of ammonia exposure on workers in a fertility factory. Indian J Exp Biol 35(5):487-492.

*Yang GY, Tominack RL, Deng JF. 1987. An industrial mass ammonia exposure. Vet Hum Toxicol 29:476-477.

Yeldandi AV, Tan X, Dwivedi RS, et al. 1990. Coexpression of glutamine synthetase and carbamoylphosphate synthase I genes in pancreatic hepatocytes of rat. Proc Natl Acad Sci U S A 87(3):881-885.

*Yoo KP, Lee SH, Lee WH. 1986. Ionization and Henry's law constants for volatile, weak electrolyte water pollutants. Korean J Chem Eng 3(1):67-72.

Zago C, Capodaglio G, Ceradini S, et al. 2000. Benthic fluxes of cadmium, lead, copper and nitrogen species in the northern Adriatic Sea in front of the River Po outflow, Italy. Sci Total Environ 246(2-3):121-137.

Zange J, Gronczewski J, Jans AW. 1993. NH_4^+ metabolism and the intracellular pH in isolated perfused rat liver. Biochem J 293:667-673.

Zejda JE, Barber E, Dosman JA, et al. 1994. Respiratory health status in swine producers relates to endotoxin exposure in the presence of low dust levels. J Occup Med 36(1):49-56.

*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

Zielinska M, Hilgier W, Law RO, et al. 1999. Effects of ammonia in vitro on endogenous taurine efflux and cell volume in rat cerebrocortical minislices: Influence of inhibitors of volume-sensitive amino acid transport. Neuroscience 91(2):631-638.

Zielinska M, Law RO, Albrecht J. 2003. Excitotoxic mechanism of cell swelling in rat cerebral cortical slices treated acutely with ammonia. Neurochem Int 43:299-303.

*Zieve L, Doiaki WM, Zieve FJ. 1974. Synergism between mercaptans and ammonia or fatty acids in the production os a coma: A possible role for mercaptans in the pathogenesis of hepatic coma. J Lab Clin Med 83:16-28.

*Zimber A, Visek WJ. 1972a. Effect of urease injections on DNA synthesis in mice. Am J Physiol 233:1004-1008.

*Zimber A, Visek WJ. 1972b. Effect of urease injections on ehrlich ascites tumor growth in mice. Proc Soc Exp Biol Med 139:43-149.

9. REFERENCES

*Zissu D. 1995. Histopathological changes in the respiratory tract of mice exposed to ten families of airborne chemicals. J Appl Toxicol 15:207-213.

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 BMD10 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.

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.

q1*—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) (TD50)—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.

APPENDIX A

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, 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, 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: Ammonia
CAS Number: 7664-41-7
Date: July 2004
Profile Status: Third Draft Post-Public
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 14
Species: Human

Minimal Risk Level: 1.7 [ ] mg/kg/day [X] ppm

Reference: Verberk MM. 1977. Effects of ammonia in volunteers. Int Arch Occup Environ Health 39:73-81.

Experimental design: The study examined the effects of exposure to ammonia in a group of 16 volunteers. Eight of them (experts) knew the effects of ammonia from the literature, but had had no personal contact, whereas the remaining eight subjects (non-experts) were students from a non-science faculty and were not familiar with ammonia or experiments in laboratory situations. All members of a group were exposed on the same day to one of the concentrations tested (50, 80, 110, or 140 ppm). The testing was repeated with a 1-week interval. Immediately before and after exposure, vital capacity, forced expiratory volume, and forced inspiratory volume were measured. During exposure, each subject recorded subjective feelings every 15 minutes as no sensation (0), just perceptible (1), distinctly perceptible (2), nuisance (3), offensive (4), or unbearable (5). No statistical analysis was performed and there was no group exposed to air only. A few weeks after the experiments, the subjects were tested to measure (pre-existing) non-specific reactivity of the airways to exogenous stimuli.

Effects noted in study and corresponding doses: None of the participants was hypersusceptible to non-specific irritants. Results of the pulmonary function tests after exposure were not statistically significantly different from pre-exposure values. For the non-experts, there was a clear increase in the number of reported symptoms for smell, eye irritation, throat irritation, cough, and general discomfort as the exposure concentration increased. The latter was not as clear for the experts. The number of symptoms recorded with a score >3 (nuisance) for smell, eye irritation, nose, throat, and urge to cough for the 50, 80, 110, and 140 ppm exposure groups was 2, 2, 7, and 11 , respectively, for the experts and 6, 12, 18, and 29, respectively, for the non-experts. It should also be mentioned that the subjective responses appeared more pronounced in the non-expert group than in the expert group.

Dose and end point used for MRL derivation: 50 ppm for mild irritation to the eyes, nose, and throat in humans exposed to ammonia gas for 2 hours.

Because the effects observed were local irritation effects, they were not time-dependent (but rather concentration-dependent), an adjustment to 24-hour exposure was not necessary.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal 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?
N/A

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

Other additional studies or pertinent information which lend support to this MRL: Although the Verberk et al. (1977) study has limitations (no statistical analysis, subjective end points, no control group), it demonstrates that concentrations of 50 ppm ammonia can produce minimal discomfort in healthy members of the general population and therefore, should be avoided. Additional relevant information is provided by a study by Ferguson et al. (1977). In that study, a group of six healthy volunteers, not previously accustomed to working in an ammonia environment, were exposed 5 days/week to 25 ppm (2 hours/day), 50 ppm (4 hours/day), or 100 ppm (6 hours/day) of ammonia, or to 50 ppm of ammonia 6 hours/day for 6 weeks. End points monitored included subjective and objective measures of eye and throat irritation as well as pulse rate, respiration rate, pulmonary function (FVC, FEV), assessment of neurological function (reflex, balance, and coordination), and body weight. The exposure protocol consisted of a pre-exposure evaluation by a physician, 3 hours of exposure (this conflicts with exposure data on table 2 of the study and mentioned above), a mid-point physician's observation, lunch break, 3 additional hours of exposure, and a third physician's observation 30 minutes after exposure ceased. The conjunctiva and mucosa of the nose and throat were examined by a physician before and after each daily exposure and the degree of irritation noted was described as mild, moderate, or marked. Exposure to ammonia had no significant effect on the measures of respiratory function or in the neurological tests conducted. The results of the evaluations of irritation conducted by the physician showed no significant differences between the exposure groups, including the 0 ppm exposure group (pre-exposure). All subjects experienced some watering of the eyes and a sensation of dryness in the nose and throat and there was one observation of definite redness in the mucosa of the nose after a 6-hour exposure to 100 ppm during which time, there was an excursion to 200 ppm ammonia. No redness was observed in this subject the following morning. Throughout the study, the physician observed 6 cases of eye irritation, 20 of nose irritation, and 9 of throat irritation, and most cases appeared to have occurred the first week of the study during exposure to 50 ppm. It is difficult to determine in this study a NOAEL or LOAEL for irritation due to the different exposure durations experienced by the subjects, but it would appear that an exposure concentration of 100 ppm ammonia for 6 hours caused no significant changes in the vital functions measured and that 50 ppm can cause eye, nose, and throat irritation.

NIOSH (1974) reviewed 15 studies of case reports in which subjects were exposed to very high, but unquantified, concentrations of ammonia. The 15 reports provided a representative array of documented clinical findings including death, permanent eye lesions, and chronic respiratory symptoms, as well as acute lower and upper respiratory symptoms. The only quantitative information available was that a worker died 6 hours after estimated exposure to 10,000 ppm ammonia for an unspecified time (Mulder and Van der Zalm 1967). Studies with volunteers, also reviewed by NIOSH (1974), generally used concentrations of ammonia much higher than those in the studies by Verberk et al. (1977) or Ferguson et al. (1977) and/or exposure durations of only minutes. For example, exposure to a concentration of 500 ppm for 30 minutes caused respiratory irritation graded as severe by 2 out 7 subjects (Silverman et al. 1949). Four out of 6 volunteers exposed to 50 ppm ammonia for 10 minutes graded the irritation as "moderate" and none described it as "discomforting" or "painful" (MacEwen et al. 1970). All of the

subjects rated the odor as “highly penetrating” at 50 ppm and 3 subjects gave the same rating to 30 ppm. IBT (1973) exposed 10 subjects to 32, 50, 72, and 134 ppm for 5 minutes and the frequency of positive findings was as follows: at 32 ppm, 1 subject complained of dryness of the nose; at 50 ppm, 2 subjects complained of dryness of the nose; at 72 ppm, 3 subjects experienced eye irritation, 2 had nasal irritation, and 3 had throat irritation; and at 134 ppm, 5 subjects had signs of lacrimation, 5 had eye irritation, 7 had nasal irritation, 8 had throat irritation, and 1 had chest irritation.

Collectively, the available information from studies in humans supports the 50 ppm exposure level from the Verberk et al. (1977) study as a minimal LOAEL for irritation in acute studies. In general, studies in animals have used higher exposure concentrations. For ammonia, a corrosive irritant gas that affects the portal of entry and produces irritation of the eyes and respiratory tract, use of human data should be preferred over animal studies.

Agency Contact (Chemical Manager): Nickolette Roney, MPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Ammonia and Ammonium Compounds
CAS Number: 7664-41-7
Date: July 2004
Profile Status: Third Draft Post Public
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 47
Species: Humans

Minimal Risk Level: 0.1 [ ] mg/kg/day [X] ppm

Reference: Holness DL, Purdham JT, Nethercott JR. 1989. Acute and chronic respiratory effects of occupational exposure to ammonia. Am Ind Hyg Assoc J 50:646-650.

Experimental design: The study evaluated sense of smell, prevalence of respiratory symptoms (cough, bronchitis, wheeze, dyspnea, and others), eye and throat irritation, and lung function parameters (FVC, FEV_1, FEV_1/FVC, FEF_{50}, and FEF_{75}) in humans exposed for an average of 12.2 years in a soda ash plant (Holness et al. 1989). The cohort consisted of 52 workers and 35 controls. The subjects were assessed on two workdays: on the first workday of their workweek and on the last workday of their workweek. Spirometry was performed at the beginning and end of each work shift, so that each worker had four tests done. To determine the exposure levels, exposed and control workers were sampled over one work shift; the average sample collection period was 8.4 hours. All of the participants in the study were males.

Effects noted in study and corresponding doses: Analysis of the results showed no significant differences in the prevalence of reported symptoms, but the exposed workers reported that exposure in the plant aggravated some of their reported symptoms (cough, wheeze, nasal complaints, eye irritation, and throat discomfort). Odor threshold was not affected by exposure to ammonia and there were no significant differences in baseline lung functions between exposed and control subjects. Analysis of each worker separately showed no significant relationship between the level of ammonia exposure and changes in lung function. Also, when the workers were divided into groups of individuals that were exposed to low (<6.25 ppm), medium (6.25–12.5 ppm), and high (>12.5 ppm) ammonia levels, no significant association was found between reporting of symptoms, decline in baseline function, or increasing decline in function over the work shift and exposure to ammonia. Furthermore, no association was evident between increasing years of exposure and decreasing lung function. However, the power of the indices of both level and length of exposure is low because only eight workers were in areas with relatively high ammonia exposure.

The MRL was calculated by adjusting the NOAEL of 9.2 ppm (the mean TWA exposure concentration) for continuous exposure (9.2 x 8/24 hours x 5/7 days) and dividing by an uncertainty factor of 10 for the protection of sensitive individuals. A modifying factor of 3 was used for the lack of reproductive and developmental studies.

Dose and end point used for MRL derivation: 9.2 ppm for no significant alterations in lung function in chronically exposed workers.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

Modifying Factors used in MRL derivation:

[X] 3 for lack of reproductive and developmental studies

Was a conversion used from ppm in food or water to a mg/body weight dose?
N/A.

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

Other additional studies or pertinent information which lend support to this MRL: Earlier studies summarized by NIOSH (1974) found that workers accustomed to 20 ppm ammonia did not complain of irritation symptoms, but showed slight redness in the conjunctiva. Those not accustomed had eye and respiratory discomfort and irritation. Another report stated that air levels below 5 ppm were associated with barely noticeable eye irritation. In yet an additional report, concentrations of 15–28 ppm in the work area produced slight eye irritation. More recent data reported respiratory effects associated with chronic-duration exposure to pollutants, including ammonia, in livestock confinement buildings and an increase in respiratory symptoms (such as bronchial reactivity/hyperresponsiveness, inflammation, cough, wheezing, or shortness of breath) and/or a decrease in lung function (such as forced expiratory volume in the first second [$FEV_{1.0}$], maximum expiratory flow rates [MEF_{50} and MEF_{75}], and maximal mid-expiratory flow rate [MMEF]) in farmers exposed to ammonia levels of 2.3–20.7 ppm (Choudat et al. 1994; Cormier et al. 2000; Donham et al. 1995, 2000; Heederik et al. 1990; Reynolds et al. 1996; Vogelzang et al. 1997, 2000). The farmers were also exposed to other possible respiratory toxins, such as dust and endotoxins. A cross-sectional study of male workers at two fertilizer factories in Saudi Arabia showed a significant association between exposure to ammonia gas and respiratory symptoms and bronchial asthma (Ballal et al. 1998). No continuous exposure levels could be calculated for these workers because the number of days worked per week was not provided. There were no chronic-duration inhalation studies in animals.

Agency Contact (Chemical Manager): Nickolette Roney, MPH

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

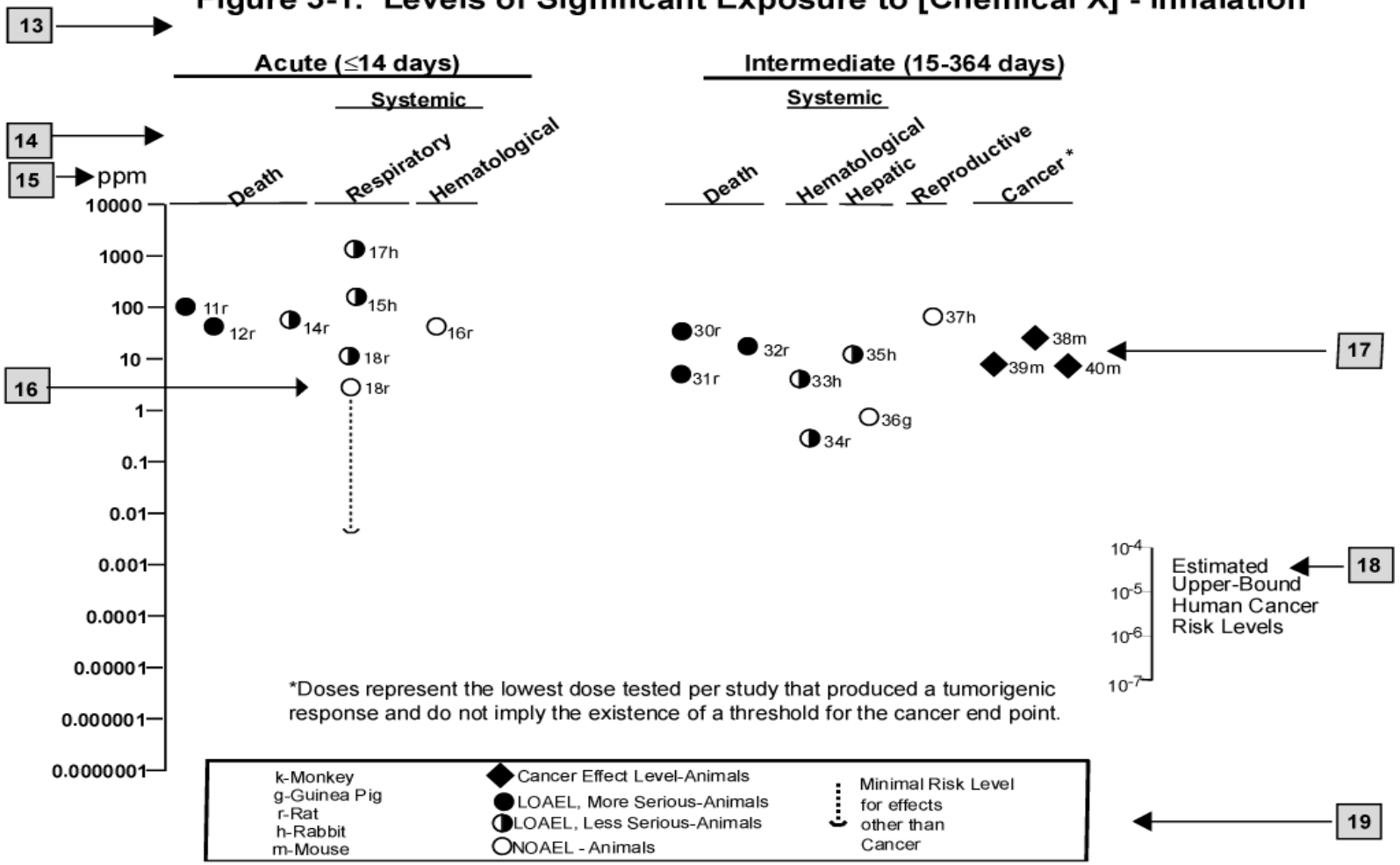
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	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