TOXICOLOGICAL PROFILE FOR ATRAZINE

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

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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 atrazine, Draft for Public Comment was released in September, 2001. This edition supersedes any previously released draft or final profile.

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE,
Mailstop E-29
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:

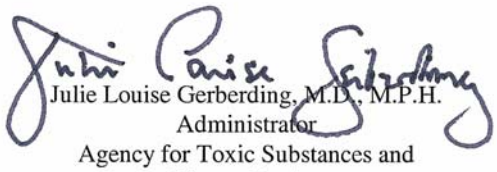
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(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 October 25, 2001 (66 FR 54014). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); and October 21, 1999 (64 FR 56792). 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:*** (404) 498-0093
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):

Alfred Dorsey, DVM
ATSDR, Division of Toxicology, Atlanta, GA

Susan S. Little, PhD
David B. Knaebel, PhD
Daniel Plewak, BS
Heather Printup, BA
Jennifer Rhoades, BA
Syracuse Research Corporation, 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 atrazine. The panel consisted of the following members:

1. James E. Klaunig, Ph.D., Professor of Pharmacology and Toxicology, Director, Division of Toxicology, Indiana University School of Medicine, 135 Bennington Drive, Zionsville, Indiana 46077;

2. Kannan Krishnan, Ph.D., Associate Professor, Department of Occupational and Environmental Health, University of Montreal School of Medicine, 2375 Chemin de la Cote Ste-Catherine, Montreal, Quebec H3T 1A8; and

3. Frederick Oehme, D.V.M, Ph.D., Professor of Toxicology, Pathobiology, Medicine, and Physiology, Director, Comparative Toxicology Laboratories, Department of Diagnostic Medicine/Pathobiology, Kansas State University, 1800 Dennison Avenue, Mosier Hall, Manhattan, Kansas 66506-5606.

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

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

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

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1. PUBLIC HEALTH STATEMENT

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

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Atrazine has been found in at least 20 of the 1,636 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which atrazine is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

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

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

1.1 WHAT IS ATRAZINE?

Atrazine is the common name for an herbicide that is widely used to kill weeds. It is used mostly on farms. Pure atrazine—an odorless, white powder—is not very volatile, reactive, or flammable. It will dissolve in water. Atrazine is made in the laboratory and does not occur naturally.

Atrazine is used on crops such as sugarcane, corn, pineapples, sorghum, and macadamia nuts, and on evergreen tree farms and for evergreen forest regrowth. It has also been used to keep

weeds from growing on both highway and railroad rights-of-way. Atrazine can be sprayed on croplands before crops start growing and after they have emerged from the soil. Some of the trade names of atrazine are Aatrex®, Aatram®, Atratol®, and Gesaprim®. The scientific name for atrazine is 6-chloro-N-ethyl-N'-(1-methylethyl)-triazine-2,4-diamine. Atrazine is a Restricted Use Pesticide (RUP), which means that only certified herbicide users may purchase or use atrazine. Certification for the use of atrazine is obtained through the appropriate state office where the herbicide user is licensed.

Certified herbicide workers (see Section 1.7) may spread atrazine on crops or croplands as a powder, liquid, or in a granular form. Atrazine is usually used in the spring and summer months. For it to be active, atrazine needs to dissolve in water and enter the plants through their roots. It then acts in the shoots and leaves of the weed to stop photosynthesis. Atrazine is taken up by all plants, but in plants not affected by atrazine, it is broken down before it can have an effect on photosynthesis. The application of atrazine to crops as an herbicide accounts for almost all of the atrazine that enters the environment, but some may be released from manufacture, formulation, transport, and disposal.

More complete information about the sources, properties, and uses of atrazine can be found in Chapters 4 and 5 of this profile.

1.2 WHAT HAPPENS TO ATRAZINE WHEN IT ENTERS THE ENVIRONMENT?

Atrazine is applied to agricultural fields or to crops to kill weeds. It is also used near highways and railroads for the same purposes. Some atrazine may enter the air after it is applied to the soil. Some atrazine may also be washed from the soil by rainfall and enter surrounding areas, including streams, lakes, or other waterways. Some atrazine may migrate from the upper soil surface to deeper soil layers and enter the groundwater.

After atrazine is applied to soils, it will remain there for several days to several months; in rare situations, it may remain in soils for a few years. However, in most cases, atrazine will be broken down in the soil over a period of one growing season. In addition to being removed from

soil, atrazine is also taken up by the plants that grow there, and this uptake is the first step in killing weeds.

Any atrazine that is washed from the soil into streams and other bodies of water will stay there for a long time, because breakdown of the chemical is slow in rivers and lakes. It will also persist for a long time in groundwater. This is one reason why atrazine is commonly found in the water collected from drinking water wells in some agricultural regions.

If atrazine enters the air, it can be broken down by reactions with other reactive chemicals in the air. However, sometimes atrazine is on particles such as dust. When this happens, breakdown is not expected to occur. Atrazine is removed from air mainly by rainfall. When atrazine is on dust particles, the wind can blow it long distances from the nearest application area. For example, atrazine has been found in rainwater more than 180 miles (300 kilometers) from the nearest application area.

Atrazine does not tend to accumulate in living organisms such as algae, bacteria, clams, or fish, and, therefore, does not tend to build up in the food chain.

More complete information about the environmental fate of atrazine can be found in Chapter 6 of this profile.

1.3 HOW MIGHT I BE EXPOSED TO ATRAZINE?

Most people are not exposed to atrazine on a regular basis. People living near areas where atrazine was applied to crops may be exposed through contaminated drinking water. Atrazine has been found at about 20 Superfund sites in the United States. People living near those sites may be exposed to higher levels of atrazine. If you are a factory worker who works with atrazine, you may be exposed to higher amounts of atrazine. The government has estimated that approximately 1,000 people may be exposed to atrazine in this way.

Atrazine, one of the most widely used herbicides in the United States, is intentionally applied to crops, especially corn, sugarcane, pineapples, and sorghum. Therefore, people who live near areas where these crops are grown, especially farm workers and herbicide applicators who apply atrazine, may be exposed to atrazine because it is used in agriculture. You may be exposed to atrazine if you are nearby when crops are treated with atrazine, if you are involved in the application of atrazine to crops, or if you are near other places where it is applied. Most of the time, atrazine is not found in high concentrations in the air, but may be found in higher concentrations in the air near disposal facilities or near areas where it is being applied to crops. You may also be exposed to atrazine by digging in dirt that has atrazine in it. Your children may be exposed to atrazine by playing in dirt that contains atrazine. You and your children may also be exposed to atrazine if you drink water from wells that are contaminated with the herbicide. While it is used on many crops, it has not been found in many food samples, and then only at very low levels. Therefore, it is very unlikely that you would be exposed to atrazine by eating any foods.

More information regarding exposure to atrazine can be found in Chapter 6.

1.4 HOW CAN ATRAZINE ENTER AND LEAVE MY BODY?

Scientists do not know how much or how quickly atrazine will be absorbed into your body if you breathe it in. If you inhale atrazine-containing dust, some of the particles may deposit in your lungs. Larger atrazine particles may deposit before reaching the lungs and be coughed up and swallowed. If your skin comes in contact with atrazine-contaminated soil or water, a small amount of it may pass through your skin and into your bloodstream. If you swallow food, water, or soil containing atrazine, most of it will pass through the lining of your stomach and intestines and enter your bloodstream.

Once atrazine enters your bloodstream (is absorbed), it is distributed to many parts of your body. Animal studies indicate that atrazine is changed in your body into other substances called metabolites. Some atrazine and its metabolites may enter some of your organs or fat, but

atrazine does not build up or remain in the body. Most of the metabolites leave your body within 24–48 hours, primarily in your urine, with a lesser amount in your feces.

More information on how atrazine enters and leaves your body can be found in Chapter 3.

1.5 HOW CAN ATRAZINE AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

One of the primary ways that atrazine can affect your health is by altering the way that the reproductive system works. Studies of couples living on farms that use atrazine for weed control found an increase in the risk of pre-term delivery. These studies are difficult to interpret because most of the farmers were men who may have been exposed to several types of pesticides. Atrazine has been shown to cause changes in blood hormone levels in animals that affected the ability to reproduce. Some of the specific effects observed in animals are not likely to occur in occur in humans because of biological differences between humans and these types of animals. However, atrazine may affect the reproductive system in humans by a different mechanism. Atrazine also caused liver, kidney, and heart damage in animals; it is possible that atrazine could cause these effects in humans, although this has not been examined.

Not enough information is available to definitely state whether atrazine causes cancer in humans. Studies of human populations indicate that there may be a link between atrazine use and some

types of cancer, but the information was not specific enough to make a definitive connection between atrazine and cancer. An increased risk of developing mammary tumors was observed in one strain of female rats. Because of biological differences between rats and humans, it is not likely that humans would develop this type of cancer following atrazine exposure. Other studies in animals did not find atrazine-related increases in cancer. The International Agency for Research on Cancer (IARC) has determined that atraine is not classifiable as to its carcinogenicity to humans based on inadequate evidence in humans and sufficient evidence in experimental animals.

More information on how atrazine can affect your health can be found in Chapter 3.

1.6 HOW CAN ATRAZINE 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 likely to be exposed to atrazine in the same way as adults, primarily through contact with dirt that contains atrazine or by drinking water from wells that are contaminated with the herbicide.

Little information is available regarding the effects of atrazine in children. Maternal exposure to atrazine in drinking water has been associated with low fetal weight and heart, urinary, and limb defects in humans. Atrazine has been shown to slow down the development of fetuses in animals, and exposure to high levels of atrazine during pregnancy caused reduced survival of fetuses. It is unclear whether or at what level of exposure this might occur in humans.

It is not known whether atrazine or its metabolites 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.

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

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

Only certain people can use atrazine because it is a Restricted Use Pesticide (RUP), so most people cannot purchase it freely or use it. Since most people cannot purchase it for private use, one way you can reduce your risk of exposure to atrazine is by avoiding areas where it is being used on crops or for control of weeds. You can also reduce your risk of exposure by avoiding digging or working in soils where it has been applied. If you live in an area where atrazine is used, you may wish to avoid being near the area when it is being applied. If children play in or near areas where it atrazine has been applied too soon after it has been applied, they can be exposed to the herbicide. You should encourage your children to not play in these areas.

Atrazine has been found in water collected from many drinking water wells in the Midwestern United States. Therefore, you may be able to reduce your risk of exposure to atrazine by ensuring that your water supply is free of atrazine, or contains no measurable levels of atrazine. Atrazine has also been found in streams, rivers, and lakes near fields where it has been applied. Higher amounts have been found in these waterways in the spring and summer months. Therefore, you may wish not to swim in, nor drink from, these bodies of water. Children may be exposed to atrazine if they play in fields where atrazine has been applied or in streams receiving runoff from those fields. They should be encouraged not to play in these fields or bodies of water. Low amounts of atrazine have also been found in carpet and house dust in homes in the Midwest. However, very few children living in these homes have had any atrazine in their bodies. To prevent possible exposure of yourself or your children to atrazine, you may wish to vacuum floors and dust surfaces on a frequent basis, especially during the spring and summer months.

If you are a worker who applies atrazine to crops or for weed control, you can reduce your exposure to atrazine by using it according to 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 ATRAZINE?

Specific and sensitive tests have been developed to detect atrazine in blood, fat, semen, and breast milk of exposed individuals. Because atrazine is removed from the body relatively quickly, these tests are only useful in detecting recent exposures (within 24–48 hours) and are not useful for detecting past exposures to atrazine. These tests currently cannot be used to estimate how much atrazine you have been exposed to or whether adverse health effects will occur. These tests are not usually performed in a doctor's office because special equipment is required and samples must be sent to a laboratory for testing.

More information on tests that detect atrazine and its metabolites can be found in Chapter 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. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated 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 atrazine include the following:

Atrazine is currently under review for pesticide re-registration by EPA. Therefore, EPA may be contacted for more information about atrazine. OSHA has set a limit of 5 mg atrazine/m^3 of workroom air for an 8-hour workday. NIOSH recommends a standard for occupational exposure of 5 mg atrazine/m^3 of workroom air during a 10-hour shift to protect workers from a concern that atrazine may cause cancer. The EPA has set a maximum amount of atrazine allowable in drinking water of 3 μg/L. In addition, atrazine is designated as a Restricted Use Pesticide, which means that only certified pesticide applicators can use atrazine. For more information, please see 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 resulting 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 information and

technical assistance toll-free number at 1-888-42ATSDR (1-888-422-8737), by email at atsdric@cdc.gov, or by writing at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop E-29
Atlanta, GA 30333
Fax: 1-404-498-0093

For-profit organizations may request a copy of final 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 ATRAZINE IN THE UNITED STATES

Atrazine is a white, odorless powder (when pure) that is used as an herbicide to stop the growth of broadleaf and grassy weeds in crops such as corn, sugarcane, sorghum, pineapples, and macadamia nuts. It is not found naturally in the environment. It is moderately soluble in water, but is more soluble in organic solvents such as acetone, chloroform, and ethyl acetate. More than 37,000 tons of atrazine were used in agricultural and weed control settings in the United States in 1997.

Atrazine is released to the environment during its production and use, with the vast majority being released as a result of its application to soils as an herbicide. Atrazine that remains in the soil degrades with half-lives of a few weeks to several months. Atrazine may migrate out of the soil in surface runoff to streams, rivers, or lakes, or it may migrate deeper into the soil and become associated with groundwater. No significant degradation of atrazine has been observed in groundwater. Half-lives of atrazine in surface waters are generally >200 days. Relatively large amounts of atrazine may volatilize from the soils into the atmosphere. In the atmosphere, no direct photolysis degradation of atrazine is expected to occur, but oxidation in the presence of hydroxyl radicals is expected, with an estimated half-life of 14 hours. Most of the atrazine found in the atmosphere is expected to be sorbed to particulates; it can be transported significant distances in the atmosphere, and has been detected >180 miles from the nearest application site.

The general population may be exposed to atrazine found in water or air, but it is rarely found in foods. When the general population is exposed to atrazine, exposure levels are expected to be very low. Maximum seasonal and average atrazine concentrations of 61.6 and 18.9 ppb, respectively, were detected during a 1993–1998 monitoring program of community water systems in the United States. Air concentrations of atrazine vary with application season; concentrations usually range from just above the detection limit of approximately 0.03 to 0.20–0.32 $\mu g/m^3$ during the application period. The concentrations of atrazine detected in foods were low (0.001–0.028 ppm) in the few samples where it was detected.

Populations residing near crops where atrazine is applied or hazardous waste disposal sites or manufacturing and processing plants may be exposed to higher than average levels of atrazine in ambient air or drinking water. As mentioned above, atrazine is mobile in soils and has been detected in a high percentage of the drinking water wells near crops where atrazine has been used. Atrazine has also been identified in at least 20 of the 1,636 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL). However, the number of sites evaluated for atrazine is not known.

2.2 SUMMARY OF HEALTH EFFECTS

Atrazine is a widely used herbicide. The general population, especially people living in the vicinity of farms, may be exposed to low levels in the air and drinking water. Occupational exposure is a concern for farmers, as several routes of exposure are likely to occur. The primary adverse health effects of atrazine exposure are reproductive/developmental effects following inhalation, oral, and dermal exposure. Data on the carcinogenicity of atrazine are inconclusive. Data regarding the health effects of atrazine in humans are limited to ecological, case-control, and cohort mortality cancer studies and reproductive/ developmental toxicity studies. The bulk of the available toxicity data is from oral exposure studies in animals.

The reproductive system and the developing organism are primary targets of atrazine toxicity. There was a possible association between atrazine use/exposure of male farmers and increased pre-term delivery, but not decreased fecundity. The lack of information on exposure levels and the concomitant exposure to other pesticides makes these studies inadequate to assess the contribution of atrazine to these effects. Several animal studies have shown that atrazine exposure disrupts estrus cyclicity and alters plasma hormone levels; these effects appear to be mediated by changes in the gonadal-hypothalamic-pituitary axis. Epidemiological studies, examining developmental end points, have found an association between Iowa communities exposed to atrazine in the drinking water and an increased risk of small for gestational age babies and other birth defects. Farm couples living year-round on farms in Ontario, Canada did not have altered sex ratios, and the risk of small for gestational age deliveries was not increased in relation to pesticide exposure. Developmental effects have been observed following pre-gestational, gestational, and lactational exposure of rat and rabbit dams or post-weaning exposure of rat pups to atrazine. The observed effects included post-implantation losses, decreases in fetal body weight, incomplete ossification, neurodevelopmental effects, and impaired development of the reproductive system.

A few epidemiology studies suggest evidence of a possible association between atrazine exposure and increased cancer risk, but many others do not, and the data are insufficient to adequately assess atrazine's carcinogenic potential. The animal data associate atrazine with early onset of mammary tumors believed to be the result of atrazine-induced acceleration of reproductive senescence. It is unlikely that the mechanism by which atrazine induces mammary tumors in female Sprague-Dawley rats is operational in humans.

A limited number of animal studies have shown that atrazine exposure may affect other end points, including systemic effects, and damage to the heart, liver, and kidneys. The primary effects are discussed in greater detail below. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on the health effects resulting from exposure to atrazine.

Reproductive Effects. Results of a survey of farm couples in Ontario, Canada, conducted to assess reproductive effects of pesticides, indicated a weak to moderate association between atrazine use in the yard and an increase in preterm delivery. Other results from this survey indicated that atrazine was not associated with any decrease in fecundity as a result of effects on spermatogenesis.

Animal studies have shown that atrazine disrupts estrus cyclicity (i.e., irregular ovarian cycling and changes in the number and/or percentage of days in estrus and diestrus) and alters plasma hormone levels in rats and pigs. These effects appear to be mediated by changes in the gonadal-hypothalamic-pituitary axis that are species-, and even strain-, specific. In Sprague-Dawley rats, atrazine accelerates the normal process of reproductive senescence, which is initiated by a failure of the hypothalamus to release levels of gonadotropin releasing hormone (GnRH) that are adequate to stimulate the pituitary to release luteinizing hormone (LH). Without sufficient LH, ovulation does not occur, estrogen levels remain high, and persistent estrus results. In other strains of rats, atrazine causes elevated progesterone levels, which leads to pseudopregnancy and persistent diestrus. In pigs, atrazine exposure decreased serum estradiol-17β (E_2) concentrations resulting in a short-term delay in the onset of estrus.

The mechanism of reproductive senescence in humans does not involve disruption of hormonal regulation, but is initiated by depletion of ova in the ovaries, which ultimately results in decreased plasma estrogen levels. Therefore, disruption of the menstrual cycle or acceleration of reproductive senescence is not anticipated to occur in humans as a result of atrazine exposure. However, it is not known whether atrazine will cause other perturbations in the hypothalamus-pituitary-gonad axis results in reproductive effects in humans.

Atrazine exposure significantly reduced serum and intratesticular levels of testosterone and ventral prostrate and seminal vesicle weights in juvenile male Sprague-Dawley rats. Female Wistar and Sprague-Dawley rats had delayed vaginal opening, and delayed uterine growth was observed in female Wistar rats.

Developmental Effects. Atrazine exposure has been associated with developmental effects in both humans and animals. An association was found between Iowa communities exposed to an average of 2.2 µg/L atrazine in the drinking water in 1984–1990 and an increased risk of intrauterine growth retardation and cardiac, urogenital, and limb reduction defects. The results of a survey of farm couples living year-round on farms in Ontario, Canada indicate that the sex ratio was not altered and the risk of small for gestational age deliveries was not increased in relation to pesticide exposure (atrazine exposure level not available).

Developmental effects in response to oral exposure to atrazine have been demonstrated in laboratory animals. Studies have shown that gestational and peripubertal exposure to atrazine has an effect on reproductive development in rats and rabbits. The effects of gestational exposure to atrazine in rats and rabbits include increased post-implantation losses, full-litter resorptions, decreased live fetuses/litters, increased prenatal loss, decreased litter size, and reduced pup weights, which could be attributed to severe maternal toxicity. Atrazine exposure in rats is also associated with delayed vaginal opening, first estrus cycle, and uterine growth for female rats and decreased prostate weight, increased incidence and severity of inflammation of the lateral prostate, increased myeloperoxidase levels in the prostate, and increased total DNA in the prostate for male rats.

Atrazine has also been shown to have an effect on the development of the nervous system in rats. Mild neurobehavioral effects were observed in female offspring of Fischer rat dams exposed to atrazine pre-mating, including increased spontaneous activity level, and male offspring had improved performance (decreased latency and increased avoidance) in avoidance conditioning trials.

Other developmental effects include incomplete ossification of the skull, hyoid bone, teeth, forepaw metacarpals, and hindpaw distal phalanges in the offspring of exposed Sprague-Dawley rats, and nonossification of forepaw metacarpals and middle phalanges, hindpaw talus and middle phalanges, and patella in the offspring of exposed rabbits. No developmental effects were noted in a two-generation study in which rats were exposed to atrazine in the diet.

Cancer. The carcinogenic potential of atrazine has been investigated in a number of epidemiology studies, including cohort studies of workers at triazines manufacturing facilities, case-control studies of farmers using atrazine or triazines, and ecological studies of populations living in agricultural areas with high atrazine use and residents living in areas with atrazine-contaminated drinking water. In most of these studies, it is likely that the individuals were exposed to atrazine via several exposure routes. For example, in the studies of farmers, the likely exposure routes are inhalation during application of atrazine, dermal during handling and use of atrazine, and possible oral exposure due to contamination of groundwater. Epidemiological data are available for a number of types of cancers; however, for most cancer types, only one study investigated the possible association. The most widely studied cancer type is non-Hodgkin's lymphoma. In general, case-control studies of farmers using atrazine (in some studies, data are only available for triazine exposures) found small elevations in the risk of developing non-Hodgkin's lymphoma; typically, the odds ratios were ≤1.5 and the 95% confidence intervals included unity. A small number of cases is a common limitation of these studies. One study pooled the data from three other studies, representing farmers in four U.S. states, to increase the statistical power of the analyses. This study found an odds ratio of 1.4 (95% confidence interval of 1.1–1.8), suggesting a weak association between atrazine exposure and increased risk of non-Hodgkin's lymphoma. To account for possible exposure to other pesticides that have been shown to induce non-Hodgkin's lymphoma, the odds ratio was adjusted for exposure to 2,4-D and organophosphate insecticides. This adjustment resulted in a small decrease in the odds ratio (1.2, 95% confidence interval of 0.9–1.7). A cohort mortality study of workers at two triazines manufacturing facilities also found an increase in the risk of non-Hodgkin's lymphoma (SMR=385; 95% confidence interval of 79–1,124). Collectively, these studies provide suggestive evidence of a possible association between atrazine exposure and non-Hodgkin's lymphoma, but a causal relationship cannot be established.

Evidence on the possible association between atrazine exposure and increased risk of other cancer types is weak. Studies of farmers or possible agricultural workers did not find significant increases in the risk of multiple myeloma, leukemia, soft tissue sarcoma/carcinoma, or Hodgkin's disease. Suggestive evidence between atrazine (or triazines) exposure and an increased risk of prostate cancer, breast cancer, and ovarian cancer have been reported. Although these data provide a suspicion of carcinogenicity, the limited number of investigations and study limitations preclude drawing conclusions regarding these cancer types.

The animal data suggest that the carcinogenicity of atrazine is species-, strain-, and sex-specific. Statistically significant earlier onset of mammary tumors or incidence of mammary tumors were observed

in female Sprague-Dawley rats, but not in female Fischer 344 rats or in female CD-1 mice. An increase in mammary tumors was observed in male Fischer 344 rats; however, it is likely that the increased tumor incidence is due to increased lifespan of the atrazine-treated animals, as compared to the controls (aged Fischer 344 rats have a high rate of spontaneous mammary tumors). The early onset of mammary tumors in female Sprague-Dawley rats is believed to be the result of atrazine-induced acceleration of reproductive senescence. Both the failure to ovulate and the state of persistent estrus lead to constant elevated serum levels of endogenous estrogen, which could result in tumor formation in estrogen-sensitive tissues. Reproductive senescence in humans involves ovarian depletion and decreased serum estrogen levels instead of decreasing hypothalamic function and increased serum estrogen levels. It is unlikely that the mechanism by which atrazine induces mammary tumors in female Sprague-Dawley rats is operational in humans.

IARC has classified atrazine as "not classifiable as to its carcinogenicity to humans" (Group 3) based on inadequate evidence in humans and sufficient evidence in experimental animals.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

There is limited information on the toxicity of inhaled atrazine. Two human studies and no animal studies were identified. The two ecological studies examined reproductive and developmental toxicity end points in farmers using atrazine (Curtis et al. 1999; Savitz et al. 1997). In both studies, the atrazine exposure was poorly characterized; no monitoring data were provided; and exposure likely involved inhalation, oral, and dermal routes. These studies are inadequate for MRL derivation.

Oral MRLs

- An MRL of 0.01 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to atrazine.

Human data on the acute toxicity to atrazine are limited to a report of an individual intentionally ingesting weed killer containing atrazine (Pommery et al. 1993). Acute-duration animal studies have primarily focused on endocrine, reproduction, and developmental end points. The endocrine effects primarily included increases in pituitary weight and alterations in levels of several reproductive hormones. Increases in pituitary weight were observed in rats receiving gavage doses of 120 mg/kg/day for 7 days

(Babic-Gomerac et al. 1989; Šimić et al. 1994). Increases in pituitary prolactin levels and decreases in serum prolactin and luteinzing hormone levels were observed in ovariectomized, estrogen supplemented female Long-Evans rats receiving gavage doses of 50 mg/kg/day and higher for 1–3 days (Copper et al. 2000) and Sprague Dawley rats receiving 300 mg/kg/day via gavage for 1–3 days (Cooper et al. 2000). Decreases in serum luteinizing hormone levels were also observed in Holtzman rats receiving gavage doses of 100 mg/kg/day on gestational days 1–8 (Cummings et al. 2000b) and decreases in prolactin release in response to pup suckling was observed in rats receiving 25 mg/kg/day on postpartum days 1–4 (Stoker et al. 1999). Increases in serum estradiol levels were observed in Sprague-Dawley rats receiving gavage doses of 200 mg/kg/day on gestational days 1–8 (Cummings et al. 2000b) and decreases in serum and intratesticular testosterone levels were observed in juvenile (aged 46–48 days) male rats exposed to 50 mg/kg/day for 3 days (Friedmann 2002). There are a limited number of other systemic effects that were reported for acute duration exposure. The most commonly reported effects were decreases in body weight gain or weight loss at doses of 50 mg/kg/day and higher in rats (Cummings et al. 2000b; Santa Maria et al. 1987; Šimić et al. 1994).

The alterations in hormone levels resulted in a number of reproductive and developmental effects including altered estrus cyclicity at 120 mg/kg/day and higher in rats (Cooper et al. 2000; Šimić et al. 1994), decreased fertility in rats at 120 mg/kg/day (Šimić et al. 1994), increased pre- and post-implantation loss in rats administered 100 mg/kg/day and higher (Cummings et al. 2000b; Infurna et al. 1988) and rabbits administered 75 mg/kg/day (Infurna et al. 1988), and delayed ossification in rat and rabbit offspring administered 70 or 75 mg/kg/day on gestational days 6–15 or 7–19, respectively. Additionally, maternal toxicity, as evidenced by decreased food consumption and body weight gain, was also observed in rabbits administered 5 mg/kg/day; at 700 and 75 mg/kg/day severe weight losses were observed in rats and rabbits, respectively (Infurna et al. 1988).

The lowest LOAEL identified in the acute toxicity database is 5 mg/kg/day for maternal toxicity (decreased body weight gain and food consumption) in rabbits receiving gavage doses of atrazine on gestational days 7–19 (Infurna et al. 1988); this study also identified a NOAEL of 1 mg/kg/day for maternal toxicity. Derivation of an acute-duration MRL using this critical effect level would be protective for the endocrine and reproductive effects that are observed at higher doses. The lowest LOAEL values for an endocrine effect or reproductive effect are 25 mg/kg/day for decreases in prolactin release in response to pup suckling (Stoker et al. 1999) and 100 mg/kg/day for pre- and post-implantation losses in rats exposed on gestational days 1–8 (Cummings et al. 2000b), respectively; both studies identified NOAEL values of 12.5 and 50 mg/kg/day, respectively.

An MRL of 0.01 mg/kg/day was derived using the NOAEL of 1 mg/kg/day, with a LOAEL of 5 mg/kg/day, for maternal toxicity (decreased body weight gain and food consumption) in New Zealand White rabbits exposed to atrazine on gestational days 7–19 (Infurna et al. 1988). The NOAEL of 1 mg/kg/day was divided by an uncertainty factor of 100 (10 to account for animal to human extrapolation and 10 for human variability).

- An MRL of 0.003 mg/kg/day has been derived for intermediate-duration oral exposure (15–365 days) to atrazine.

No studies have examined the intermediate-duration oral toxicity of atrazine in humans. In animals, intermediate-duration oral exposure has resulted in reproductive, developmental, immunological, and a variety of systemic effects. Atrazine disrupts the normal functioning of the endocrine system resulting in impaired reproduction and hormone levels. A decrease in pituitary weights were observed in juvenile rats exposed to 12.5 mg/kg/day on postnatal days 22–41 (Laws et al. 2000). Alterations in endocrine hormones included decreases in serum luteinizing hormone levels in rats at 75 mg/kg/day (Cooper et al. 2000); increases in pituitary prolactin levels in rats at 75 mg/kg/day (Cooper et al. 2000); alterations in estradiol levels in rats at 6.9 mg/kg/day and higher (Cooper et al. 2000; Eldridge et al. 1994a; Wetzel et al. 1994) and pigs at 1 or 2 mg/kg/day (Gojmerac et al. 1996, 1999); and decreases in testosterone levels at 50 mg/kg/day and higher (Friedmann 2002; Trentacoste et al. 2001). These hormone alterations resulted in a disruption of estrus cyclicity in pigs exposed to 1 or 2 mg/kg/day (Ćurić et al. 1999; Gojmerac et al. 1999) and rats exposed to 6.9 mg/kg/day and higher (Cooper et al. 1996b; Eldridge et al. 1994a, 1994b; Wetzel et al. 1994). Decreases in ovarian and uterine weights were also observed in rats at 100 mg/kg/day (Eldrigde et al. 1994a) and ovarian lesion were observed in pigs at 2 mg/kg/day (Ćurić et al. 1999; Gojmerac et al. 1996). Postnatal exposure to atrazine also results in impaired development of the reproductive system; delayed vaginal opening and delayed preputial separation were observed in rat offspring at 50 (Laws et al. 2000) and 12.5 mg/kg/day (Stoker et al. 2000), respectively.

Several other effects have been observed in rats and pigs following intermediate-duration oral exposure to atrazine, including degeneration of myocardial fibers and mild degeneration and inflammation and mild chronic interstitial hepatitis in pigs at 2 mg/kg/day (Ćurić et al. et al. 1999), lymphopenia in rats at 15.4 mg/kg/day (Vos and Krajnc 1983), lymphoid depletion in lymph nodes and spleen in pigs at 2 mg/kg/day (Ćurić et al. 1999), and decreases in body weight gain in rats exposed to 2.7 mg/kg/day and higher (Cantemir et al. 1997; Cooper et al. 1996b, 2000; Desi 1983; Eldridge et al. 1994a; Laws et al. 2000; Trentacoste et al. 2001; Wetzel et al. 1994).

These studies clearly identify endocrine disruption, as evidenced by altered hormone levels and disrupted estrus cyclicity, as the most sensitive target of atrazine toxicity; the lowest LOAEL for this effect was identified in pigs. A 19-day exposure to 1 mg/kg/day atrazine in the diet resulted in a short-term delay in the onset of estrus (Gojmerac et al. 1999); a NOAEL was not identified. The delay in estrus was accompanied by significant alterations in estradiol levels, which were measured for 5 consecutive days after exposure termination (beginning 2 days prior to anticipated estrus). As presented in figure 2 of the paper (Gojmerac et al. 1999), the estradiol levels were steadily increasing on days 1 and 2, which is the pattern that would be anticipated if the animals were about to go into estrus.

An intermediate-duration oral MRL of 0.003 mg/kg/day was derived using the LOAEL of 1 mg/kg/day for delayed estrus in pigs (Gojmerac et al. 1999). This LOAEL was divided by an uncertainty factor of 300 (10 to account for the use of a LOAEL, 10 for animal to human extrapolation, and 3 for human variability). An uncertainty factor of 3 for human variability was used instead of 10 because the critical effect was identified in a sensitive population (young, developing female pigs).

Two human studies involving chronic exposure to atrazine were identified (Munger et al. 1992b, 1997). Both studies examined potential developmental effects in residents exposed to elevated triazine levels in drinking water. These studies have limited usefulness for risk assessment because atrazine concentrations were not measured and the community was exposed to a number of chemicals from the drinking water. A number of animal studies have examined the chronic toxicity of atrazine. As with acute- and intermediate-duration exposure, the endocrine/reproductive system is the primary target of toxicity. An increased length of estrus was observed in rats exposed to 6.9 mg/kg/day atrazine in the diet for 18 months (Wetzel et al. 1994); a NOAEL for this end point was not identified.

In addition to the endocrine/reproduction effects, a number of systemic effects have been observed. Decreases in body weight gain were observed in rats exposed to 25 mg/kg/day and higher (EPA 1984f, 1987d, 1987c; Pintér et al. 1990); cardiac effects consisting of increased thrombi in mice at 247 mg/kg/day and EKG alterations, atrial dilatation, fluid-filled pericardium, enlarged heart, and atrophy of atrial myocardium in dogs at 34 mg/kg/day (EPA 1987f); alterations in hepatic and renal clinical chemistry parameters in rats at 52 mg/kg/day (EPA 1984f, 1987d); and hematological alterations in rats at 71 mg/kg/day (EPA 1984f, 1987d), mice at 194 mg/kg/day (EPA 1987b), and dogs at 34 mg/kg/day (EPA 1987f).

The lowest LOAEL identified in a chronic study was 6.8 mg/kg/day for increased estrus cycle length in rats (Wetzel et al. 1994). This study was not selected as the basis for a chronic-duration oral MRL because the resultant MRL would be higher than the MRL for intermediate-duration exposure.

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 atrazine. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of atrazine are indicated in Table 3-1 and Figure 3-1.

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

No studies were located regarding death in humans and/or animals after inhalation exposure to atrazine.

3.2.1.2 Systemic Effects

No studies were located regarding systemic effects in humans or animals after inhalation exposure to atrazine.

3.2.1.3 Immunological and Lymphoreticular Effects

Altered immunological parameters have been observed in male Fischer-344 (F344) rats receiving a single 30 mg/kg intratracheal dose of atrazine (Hurbankova et al. 1996). One week after exposure, statistically significant changes included increased number of aveolar macrophages; decreased percent of active phagocytes; increased lactate dehydrogenase in bronchoalveolar lavage and serum; decreased percent of monocytes in blood; increased lactate dehydrogenase in serum; and increased acid phosphate in serum. Three months after exposure, the percent of active phagocytes and acid phosphatase levels in serum were still statistically significantly altered.

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans and/or animals after inhalation exposure to atrazine.

3.2.1.5 Reproductive Effects

Results of a survey of farm couples in Ontario, Canada, to assess reproductive effects of pesticides indicated an association between atrazine use in the yard with an increase in preterm delivery (Arbuckle et al. 2001; Savitz et al. 1997). Other results from this survey of Ontario farm couples indicated that atrazine was not associated with any decrease in fecundity as a result of effects on spermatogenesis (Curtis et al. 1999). In these cohort studies, it is probable that the application of atrazine involved both dermal and inhalation exposure. The men performed most of the farm activities that involved pesticide use; most of the women were indirectly exposed, possibly through contact with contaminated clothing or by consuming contaminated drinking water.

A survey of 1,898 farm couples living year-round on farms in Ontario, Canada, assessed reproductive effects of pesticides by comparing the pregnancies in which the men used pesticides during the 3 months prior to conception, to the referent group, which consisted of pregnancies in which the men had no farming or chemical activity in the 3 months prior to conception (Savitz et al. 1997). The use of atrazine as a yard herbicide, but not the use as a crop herbicide, was significantly associated with an increase in preterm delivery after adjusting for mother's age, education, income, occupation, ethnicity, use of tobacco

and caffeine during pregnancy, primary language, and month of conception (OR=4.9, 95% CI=1.6–15; OR=2.4, 95% CI=0.8–7.0, respectively). There was no significant association with crop herbicide activity and yard herbicide activity using atrazine with miscarriage (pregnancy loss before 20 weeks of gestation) (adjusted OR=1.5, 95% CI=0.9–2.4 and OR=1.2, 95% CI=0.6–2.3, respectively). The risk of small for gestational age deliveries was not increased in relation to pesticide exposure and sex ratio was not altered. Farm activities, pesticide use, and pregnancy outcome were self-reported, no specific exposure levels were available, and other pesticides were used during the period when atrazine was used; therefore, it was not possible to make a definite correlation between observed effects and atrazine exposure.

A related study of Ontario farm couples analyzed the effect of pesticide exposure on the risk of spontaneous abortion (Arbuckle et al. 2001). Exposures were considered separately for preconception (3 months before and up to 1 month of conception) and postconception (first trimester) and for early (<12 weeks) and late (12–19 weeks) spontaneous abortions. Pesticides were divided into use classes, chemical family, and active ingredient categories, and were considered separately. A total of 2,110 women provided information on 3,936 pregnancies, including 395 spontaneous abortions. The occurrence of spontaneous abortion was self-reported. The women were asked to recall how many weeks pregnant they were at the time of the incidence as well as other information considered in the study, including demographic and lifestyle information, pesticides currently and historically used on the farm and around the home, medical history, and complete reproductive history. The majority of pesticide application was done by the men; only 20% of the women reported direct handling of the pesticides. There was no significant increase in risk of early (<12 weeks) or late (12–19 weeks) spontaneous abortion (OR=1.3, 95% CI=0.8–2.0 and OR=1.1, 95% CI=0.7–1.9, respectively) in women who were exposed to atrazine prior to conception. Post-conception exposures served as the referent in assessing the importance of the timing of exposure to the risk of spontaneous abortion. Women age 35 and older who were exposed to triazines preconception had 3 times the risk of spontaneous abortion (OR=2.7, 95% CI=1.1–6.9) compared to women of the same age who were not exposed. There was no observed increased risk of spontaneous abortion associated with postconception exposure to atrazine.

Another study of 1,048 Ontario farm couples, reporting 2,012 pregnancies, was conducted during 1991–1992 to assess the influence of pesticide exposure on time to pregnancy (Curtis et al. 1999). Pesticide exposure was defined as pesticide use on the farm during the month of trying to conceive or at any time during the prior 2 months (the time in which spermatogenesis may have been affected). The study only included women who planned and became pregnant. A number of confounders were

controlled for, including age when trying to conceive, ethnicity, smoking, caffeine consumption, alcohol use, diseases or drugs that may affect fertility, working at a hazardous job off the farm, recent full-term pregnancies, breastfeeding, method of contraception discontinued when beginning to attempt pregnancy, body mass index, and gestational age at pregnancy diagnosis. Atrazine was not associated with any decrease in fecundity; the adjusted odds ratios were 1.06 (95% CI=0.64–1.74) and 0.97 (95% CI=0.79–1.17) for women directly exposed to atrazine and women without direct exposure (indirect male exposure), respectively.

No studies were located regarding reproductive effects in animals after inhalation exposure to atrazine.

3.2.1.6 Developmental Effects

The results of a survey of 1,898 farm couples living year-round on farms in Ontario, Canada, designed to assess reproductive effects of pesticides, indicated that the sex ratio was not altered and the risk of small for gestational age deliveries was not increased in relation to pesticide exposure (atrazine exposure level not available) (Savitz et al. 1997). It is probable that the pesticide application resulted in both dermal and inhalation exposure.

No studies were located regarding developmental effects in animals after inhalation exposure to atrazine.

3.2.1.7 Cancer

A retrospective cohort study was conducted to investigate the mortality of workers from two triazine manufacturing plants located in Alabama (major products are agricultural chemicals including triazines) and Louisiana (major products are triazine herbicides) from 1960 to 1986 (Sathiakumar et al. 1996). Vital status of the cohort was ascertained as of January 1, 1987 from records obtained from the two plants, the Social Security Administration, the Department of Motor Vehicles, and the National Death Index. Based on job information of workers from both plants, including period of employment, job title, and work area, a subgroup of 4,917 male workers was identified as having definite/probable (n=2,683) or possible (n=2,234) triazine exposure. Overall, there were 220 deaths observed compared to 253 expected according to U.S. mortality rates (standardized mortality ratio [SMR]=87; 95% CI=75–99). Deaths from cancer were also similar to U.S. rates (SMR=106; 95% CI=76–142). Of those with definite or probable triazine exposure, the SMR (385; 95% CI=79–1124) was elevated for non-Hodgkin's lymphoma

(3 deaths observed versus 0.78 expected); however, two of the three observed deaths were males with <1 year of definite triazine-related work. Limitations of this study include young age of cohort, short duration of follow-up (median of 16 years), and the lack of control for exposure to other pesticides.

Several case-control studies were located regarding cancer incidence and exposure of humans to atrazine or to triazine herbicides in general. Although the exposure route was not specified in these studies, it is probable that inhalation (e.g., application of atrazine), dermal (e.g., handling and use of atrazine), and perhaps even oral (e.g., due to groundwater contamination) exposure occurred. Although limitations of these studies include lack of specific exposure data, recall error, small number of exposed cases and controls, and exposure to other chemicals, these studies nevertheless provide some suggestive evidence of an association between atrazine and some forms of cancer in humans.

An ecological study that assessed the correlation of the amount of atrazine (in pounds) used in 58 California counties to the incidence rates of each of several cancer types (non-Hodgkin's lymphoma, leukemia, soft-tissue sarcoma, brain cancer, prostate cancer, and testicular cancer) found a correlation between atrazine use and some cancers in certain ethnic groups (Mills 1998). The correlation coefficients for brain and testis cancers and leukemia in Hispanic males were r=0.54, r=0.41, and r=0.40, respectively; although the 95% CI was not reported, the study author noted that the confidence interval included zero. Hispanic females had positive correlations for non-Hodgkin's lymphoma (r=0.12) and leukemia (r=0.27); the 95% confidence intervals included zero. For prostate cancer in black males, the correlation coefficient was r=0.67 (95% CI=0.01–0.92). Limitations of this study include that no individual exposure data were available, no latency period was allowed for between potential exposure and cancer diagnosis, and there was possible exposure to a number of other pesticides.

Data from 173 adult (≥30 years of age) white men in Iowa with histologically diagnosed multiple myeloma during 1981–1984 and 650 age- and vital-status-matched white male controls were analyzed to determine the association between general farming activities and use on the farm of 24 animal insecticides, 34 crop insecticides, 38 herbicides (including atrazine), and 16 fungicides and the risk of multiple myeloma (Brown et al. 1993). Cases were identified through the Iowa Health Registry. Information on pesticide use was obtained through questionnaires and interviews, and included the first and last year the pesticide was used, whether the subject personally handled, mixed, or applied the pesticide, and whether protective equipment was used. Risks for multiple myeloma were not increased significantly for farmers who personally handled, mixed, or applied atrazine (number of cases=12; number of controls=74; OR=0.8, 95% CI=0.4–1.6).

Another case-control study of multiple myeloma and triazine use (atrazine exposure level not identified) in Iowa was conducted by Burnmeister (1990). Cases were ascertained from the State Health Registry of Iowa for males with histologically confirmed multiple myeloma who were diagnosed in 1982–1984. Information was gathered through personal interviews with farmers (n=175) and male controls who were matched for age group, vital status, and year of death (for deceased cases). A non-significant ($p>0.05$) increased OR of 1.29 (95% CI not reported) was found.

Results from a population-based case-control study of 201 white men (≥21 years old) in 66 counties in eastern Nebraska who had histologically confirmed non-Hodgkin's lymphoma indicated that there was an association between atrazine use and non-Hodgkin's lymphoma (Weisenburger 1990). Cases were identified through the University of Nebraska Lymphoma Study Group Registry and area hospitals and physicians. Controls (n=725) were selected from the same 66 counties and were matched for age, sex, race, and vital status. Based on data obtained from telephone interviews of cases and controls, it was determined that there was an elevated risk of non-Hodgkin's lymphoma associated with atrazine use (OR=1.4, 95% CI=0.8–2.2). The risk for non-Hodgkin's lymphoma increased with duration of atrazine use (OR=0.9, 0.8, 2.0, and 2.0 for use 1–5, 6–15, 16–20, and 21+ years, respectively.

A population-based case-control study was conducted in Iowa and Minnesota to determine the association between pesticide exposure (including atrazine) and leukemia (Brown et al. 1990). Cases of histologically confirmed leukemia, diagnosed in 1981–1984, were identified through review of records from the Iowa State Health Registry and Minnesota hospitals and pathology labs. Cases in four large Minnesota cities with little farming activity (Minneapolis, St. Paul, Duluth, and Rochester) were excluded from the study. Interviews were conducted with 578 white male farmers with leukemia (aged ≥30 years) and 1,245 white male controls who were matched for age, vital status, and state of residence to obtain data on medical history, farming practices, and pesticide use. The risk of leukemia for farmers who mixed, applied, or handled triazines (OR=1.1; 95%CI=0.8–1.5; number of cases=67; number of controls=172) or atrazine (OR=1.0; 95% CI=0.6–1.5; number of cases=38, number of controls=108) was not significantly increased.

Cantor et al. (1992) conducted a similar population-based case-control study in Iowa and Minnesota to determine whether there was an association between non-Hodgkin's lymphoma and exposure to pesticides, including atrazine. Histologically confirmed non-Hodgkin's lymphoma cases diagnosed during the period of 1980–1983 of white male farmers aged 30 or older were ascertained through the

Iowa State Health Registry and Minnesota hospitals and pathology labs. Patients who resided in four large cities in Minnesota (Minneapolis, St. Paul, Duluth, and Rochester) at the time of diagnosis were excluded. Data were obtained through interviews of 622 farmers with non-Hodgkin's lymphoma and 1,245 white male controls (same control group as in the Brown et al. 1990 study above) who were matched for age, vital status, and state of residence. The interviews included questions on medical history, occupational and farming practices, and pesticide use. There was no significant increase in the risk of non-Hodgkin's lymphoma for farmers who mixed, applied, or handled triazines (OR=1.2; 95% CI=0.8–1.6; number of cases=64; number of controls=133) or atrazine (OR=1.2; 95% CI=0.9–1.8; number of cases=59; number of controls=108).

Risks of soft tissue carcinoma, Hodgkin's disease, and non-Hodgkin's lymphoma associated with herbicide exposure were investigated by Hoar et al. (1986). Although the study was designed to determine the association of phenoxyacetic acids with these types of cancers, exposure to triazines (but not specifically atrazine) was also considered. White male residents of Kansas with histologically confirmed soft tissue carcinoma (n=133), Hodgkin's disease (n=132), and non-Hodgkin's lymphoma (n=170) were identified from the University of Kansas Data Service. Cases were ≥21 years old and were diagnosed in 1976–1982. Interviews gathering detailed information on farming practices, including frequency and duration of herbicide use, were conducted with cases or their next-of-kin as well as with 948 white male controls matched for age and vital status. In addition, pesticide suppliers for 110 cases were surveyed to corroborate self-reported pesticide use. Following adjustment for age, no increased risk of soft tissue carcinoma (OR=0.9; 95% CI=0.5–1.6) or Hodgkin's disease (OR=0.9; 95% CI=0.5–1.5) was associated with herbicide use. An odds ratio of 2.5 (95% CI=1.2–5.4) was found for non-Hodgkin's lymphoma and exposure to triazines and other herbicides (number of cases=14; number of controls=43). After adjusting for phenoxyacetic acids or uracils, the odds ratio was reduced to 2.2 (95% CI=0.4–9.1; number of cases=3; number of controls=11).

The relationship between herbicide (neither triazine nor atrazine exposure was specified) use on farms in 66 eastern Nebraska counties and non-Hodgkin's lymphoma was investigated by Zahm et al. (1990). Telephone interviews were conducted with 201 white males (age ≥21 years) with histologically confirmed non-Hodgkin's lymphoma (diagnosed in 1983–1986) and 831 white male controls matched for age and vital status. Herbicide use was associated with an increased risk (OR=1.3; 95% CI=0.8–2.0) of non-Hodgkin's lymphoma (attributed by the study authors mainly to the handling of phenoxyacetic acids).

Zahm et al. (1993a) performed a combined analysis of data gathered from three previous case-control studies of atrazine exposure and non-Hodgkin's lymphoma: one in eastern Nebraska (Zahm et al. 1990), one in Kansas (Hoar et al. 1986), and one in Iowa-Minnesota (Cantor et al. 1992) (see above for descriptions of each of these studies). The age-adjusted ORs for farmers using atrazine were 1.4 (95% CI=0.8–2.5; 29 cases, 69 controls) for Nebraska, 1.2 (95% CI=0.8–1.8; 52 cases, 90 controls) for Iowa, 1.4 (95% CI=0.9–2.2; 36 cases, 53 controls) for Minnesota, and 2.7 (95% CI=1.2–5.9; 13 cases, 37 controls) for Kansas. In all states combined, 130 cases and 249 controls reported atrazine farm use; the age- and state-adjusted odds ratio was 1.4 (95% CI=1.1–1.8); the age-adjusted only odds ratio was 1.5 (95% CI=1.1–1.9). The risk of diffuse type non-Hodgkin's lymphoma was higher (age- and state-adjusted OR=1.6; 95% CI=1.1–2.2) than follicular type non-Hodgkin's lymphoma (age- and state-adjusted OR=1.3; 95% CI=0.9–1.9). Contrary to expectations, the risk of non-Hodgkin's lymphoma in all states combined were greater among farmers who used atrazine but did not personally handle it in their practices (OR=1.6, 95% CI=1.0–2.4) than among those who did personally handle atrazine (OR=1.4, 95% CI=1.0–1.8). Adjustment for use of 2,4-dichlorophenoxyacetic acid (2,4-D) and organophosphate insecticide resulted in a large decrease of the OR for farmers in Nebraska (OR=0.7; 95% CI=0.3–1.3), a slight decrease for farmers in Minnesota (OR=1.3; 95% CI=0.8–2.2) and Kansas (OR=1.9, 95% CI=0.8–4.5), and an increase in Iowa (OR=1.6; 95% CI=0.9–2.9); the age-, state-, and 2-4-D and organophosphate insecticide use-adjusted odds ratios for all states combined was 1.2 (95% CI=0.9–1.7). For farmers in Nebraska with long-term exposure to atrazine, the age-adjusted odds ratios were 2.7 (5 cases, 8 controls) and 2.5 (7 cases, 11 controls) for 16–20 years and ≥21 years of use, respectively. However, adjustment for 2,4-D and organophosphate insecticide use decreased the odds ratios to 0.6 and 0.8 for farmers with 16–20 and ≥21 years of atrazine use, respectively. The only odds ratio that did not fall below unity was for farmers who used atrazine for more than 21 days/year; the age-adjusted odds ratio was 3.1 and the age- and 2,4-D and organophosphate use-adjusted odds ratio was 1.4; however, this frequency category only included one case and one control.

A population-based case-control study was conducted to determine the association between atrazine exposure and the risk of non-Hodgkin's lymphoma in women who lived or worked on farms in 66 counties of eastern Nebraska (Zahm et al. 1993b). Cases were identified from the University of Nebraska Lymphoma Study Group and area hospitals. White women (age ≥21 years) with histologically confirmed cases of non-Hodgkin's lymphoma (or their next-of-kin) and white female controls (matched for county of residence, race, vital status, and age) were interviewed to determine medical history, pesticide use, application method, use of protective equipment, and how often the pesticides were personally handled. Interviews were completed for 134 of 206 cases and 707 of 824 controls. The OR

for women living on a farm where atrazine was used was 1.4 (95% CI=0.6–3.0) with 11 cases and 31 controls. For women who reported having personally used atrazine, the OR was 2.2 (95% CI=0.1–31.5, one case and two controls). Very few women examined in this study reported personally handling pesticides; indirect exposure (e.g., handling pesticide-contaminated clothing or through contaminated drinking water) to atrazine was more likely.

The association between colon cancer and triazine use was explored by Hoar et al. (1985) in a case-control study of Kansas farmers. Information on pesticide exposure was gathered via interviews with 57 histologically confirmed colon cancer cases (identified in 1976–1982) and 948 controls. Only 2 cases and 43 controls had confirmed triazine exposure (atrazine exposure not specified). An association between colon cancer and triazine exposure was not found in this study (OR=1.4; 95% CI=0.2–7.9).

Exposure of Italian female farmers to the chemical class, triazines (atrazine exposure not specified), was associated with a significant increased risk for ovarian neoplasms in a case-control study conducted by Donna et al. (1989). The women lived in an Italian province where triazine herbicides were used in farming practices. Cases were women with epithelial ovarian cancer diagnosed during the period of 1980–1985 identified from 18 area hospitals. Interviews with 65 cases and 126 female age-matched controls provided data on herbicide use, farming activity, and reproductive factors. Subjects were then classified by the authors as having definite, possible, or no exposure to herbicides. The odds ratios, adjusted for age, number of live births, and use of oral contraceptives, were 2.7 (90% CI 1.0–6.9) for those ‘definitely’ exposed (7 cases and 7 controls) and 1.8 (90% CI 0.9–3.5) for those ‘possibly’ exposed (14 cases and 20 controls).

Donna et al. (1984) conducted a hospital-based study of 60 women in Piedmont, Italy who were diagnosed between 1974 and 1980 with histologically confirmed primary mesothelial ovarian tumors. Personal interviews were conducted with cases and 127 controls diagnosed with other types of cancer to determine residence and occupational history as well as herbicide exposure (categorized as definite, probable, or no herbicide exposure). Although no data were provided specifically for atrazine or triazines, there was an increased risk of ovarian cancer with herbicide use (OR=4.4, 95% CI=1.9–16) based on 8 cases and no controls with ‘definite’ herbicide exposure and 10 cases and 14 controls with ‘probable’ herbicide exposure.

The overall evidence from epidemiological studies indicates that there is a slightly increased risk of non-Hodgkin’s lymphoma among farmers exposed to atrazine. There is also suggestive evidence of weak

associations between triazine/atrazine exposure and the increased risk of prostate, breast, and ovarian cancers. Significant increases in the risk of other forms of cancer (i.e., multiple myeloma, leukemia, soft tissue sarcoma/carcinoma, and Hodgkin's disease) were not found after exposure to atrazine or triazines.

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

3.2.2 Oral Exposure

3.2.2.1 Death

The available information on the lethality of atrazine in humans is limited to a case report of a man intentionally ingesting 500 mL weed killer containing 100 g of atrazine, 25 g of aminotriazole, 25 g of ethylene glycol, and 0.15 g of formaldehyde (Pommery et al. 1993); the approximate amount of atrazine ingested was 1,429 mg/kg. The man exhibited coma, circulatory collapse, metabolic acidosis, and gastric bleeding, and died 3 days later. The study authors stated that some of the symptoms displayed by the patient upon hospital admission (metabolic acidosis and large anion gap) indicated that ethylene glycol was an important toxicant. Ethylene glycol was present in the blood (300 mg/L), and formic and oxalic acids were detected in the urine. The study authors also speculated that aminotriazole and possibly formaldehyde, as well as atrazine, may have contributed to the symptoms and ultimate outcome of the case.

Atrazine has a low acute toxicity in laboratory animals. Exposure of pregnant Charles River rats to 700 mg/kg/day atrazine in the commercial product, Aatrex, throughout gestation resulted in 78% mortality; the cause of death was not determined (Infurna et al. 1988). Acute oral LD_{50} values for adult male and female rats of 1,471 and 1,212 mg/kg (Ugazio et al. 1991b) and 737 and 672 mg/kg (Gaines and Linder 1986), respectively, have been reported. An LD_{50} of 2,310 mg/kg was reported for young (weanling) male rats (Gaines and Linder 1986), indicating a lower sensitivity to atrazine than adult rats. A significant increase in mortality was observed in female Sprague-Dawley rats exposed to 39 or 71 mg/kg/day atrazine for up to 24 months (EPA 1986; Wetzel et al. 1994); mortality was not affected in similarly exposed female F344 rats (Wetzel et al. 1994). Survival was statistically decreased in female mice receiving 247 or 483 mg/kg/day atrazine in the diet for ≥91 weeks; similar exposure of male mice did not affect mortality (EPA 1987b; Stevens et al. 1999).

Cattle that consumed an unknown quantity of spilled Aatrex (containing 76% atrazine) became ill and one became recumbent and died within 8 hours (Jowett et al. 1986). Necropsy results revealed edematous lungs and a froth in the trachea. Six other cattle died within 3 days after exhibiting anorexia, salivation, tenesmus, stiff gait, and weakness.

3.2.2.2 Systemic Effects

No studies were located regarding systemic effects in humans after oral exposure to atrazine. The highest NOAEL values and all LOAEL values from each reliable study for the systemic effects of atrazine in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. These studies are discussed below.

Respiratory Effects. No animal studies were located that evaluated respiratory function. Mice gavaged with a single dose of 875 mg/kg atrazine (Fournier et al. 1992), sheep that consumed hay sprayed with atrazine (approximately 47 mg atrazine/kg body weight/day) for 25 days (Johnson et al. 1972), and pigs treated with 2 mg/kg/day atrazine in the feed for 19 days (Ćurić et al. 1999) had no gross or histopathological lesions of the lungs. Chronic exposure of male and female rats to up to 52 and 71 mg/kg/day atrazine, respectively, in the diet also had no gross or histopathological lung lesions (EPA 1984f, 1987d).

Cardiovascular Effects. Alterations in electrocardiograph measures and heart pathology were observed in dogs exposed to about 34 mg/kg/day in the diet for 52 weeks (EPA 1987f). Observed electrocardiographic changes consisted of slight to moderate increases in heart rate (primarily in males), moderate decreases in P-II values in both sexes, moderate decreases in PR values, slight decreases in QT values, atrial premature complexes in one female, and atrial fibrillation in both sexes. Gross postmortem examination revealed moderate to severe dilatation of right and/or left atria in the majority of animals, and some dogs had fluid-filled pericardium and enlarged heart. Atrophy and myolysis of atrial myocardium and edema of the heart were also observed in these dogs. No cardiac abnormalities were observed at 5 mg/kg/day. These cardiac effects are supported by the finding of degeneration of a small number of myocardial fibers in pigs exposed to 2 mg/kg/day atrazine in the feed for 19 days (Ćurić et al.

Table 3-1 Levels of Significant Exposure to Atrazine - 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	Rat (Sherman)	1x (GO)				737 M (adult LD50) 2310 M (weanling LD50) 672 F (adult LD50)	Gaines and Linder 1986 technical grade
2	Rat (Sprague-Dawley)	Gd 6-15 1x/d (GW)				700 (78% pregnant females died)	Infurna et al. 1988 Aatrex
3	Rat (NS)	1x (GW)				1471 M (LD50) 1212[b] F (LD50)	Ugazio et al. 1991b Fogard 45% atrazine and purified
	Systemic						
4	Rat (Fischer- 344)	7d 1x/d (GO)	Endocr	60	120 (increased pituitary weight; impaired testosterone metabolism in pituitary and hypothalamus)		Babic-Gojmerac et al. 1989 recrystallized
5	Rat (Long-Evans)	1x (GW)	Endocr	200	300 (decreased serum LH and prolactin)		Cooper et al. 2000 97.1% pure
			Bd Wt	300			
6	Rat (Sprague-Dawley)	1x (GW)	Endocr	300			Cooper et al. 2000 97.1% pure
			Bd Wt	300			

Table 3-1 Levels of Significant Exposure to Atrazine - 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
7	Rat (Long-Evans)	3d 1x/d (GW)	Endocr		50	(decreased serum LH and prolactin; increased pituitary prolactin)			Cooper et al. 2000 97.1% pure
			Bd Wt	300					
8	Rat (Sprague-Dawley)	3d 1x/d (GW)	Endocr	200	300	(decreased serum prolactin levels)			Cooper et al. 2000 97.1% pure
			Bd Wt	300					
9	Rat (Long-Evans)	1x (GW)	Endocr	300					Cooper et al. 2000 97.1% pure
10	Rat (Long-Evans)	3d 1x/d (GW)	Endocr		300	(effects on neuroendocrine regulation)			Cooper et al. 2000 97.1% pure
11	Rat (Holtzman)	Gd 1-8 (GW)	Endocr	50	100	(decreased serum progesterone and LH)			Cummings et al. 2000b 97.1% pure
			Bd Wt				50	(43% decrease in body weight gain)	
12	Rat (Sprague-Dawley)	Gd 1-8 (GW)	Endocr		200	(increased serum estradiol)			Cummings et al. 2000b 97.1% pure
			Bd Wt	50			100	(69% decrease in body weight gain)	

Table 3-1 Levels of Significant Exposure to Atrazine - 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
13	Rat (Long-Evans)	Gd 1-8 (GW)	Endocr	50	100	(decreased serum LH)			Cummings et al. 2000b 97.1% pure
			Bd Wt				50	(57% decrease in body weight gain)	
14	Rat (Fischer- 344)	Gd 1-8 (GW)	Endocr	100	200	(decreased serum LH)			Cummings et al. 2000b 97.1% pure
			Bd Wt	50			100	(74% decrease in body weight gain)	
15	Rat (Sprague-Dawley)	1x/d pnd 46-48 (GO)	Endocr		50 M	(reduced serum and intratesticular testosterone levels)			Friedmann 2002
16	Rat (Sprague-Dawley)	Gd 6-15 1x/d (GW)	Bd Wt	70			700	(severe maternal body weight loss)	Infurna et al. 1988 Aatrex
17	Rat (Wistar)	6 or 12d 1x/d (GW)	Endocr		240	(decreased serum T3 and histological changes in the thyroid)			Kornilovskaya et al. 1996 95% pure
18	Rat (Fischer- 344)	12d every 48hr (GO)	Bd Wt	120					Peruzovic et al. 1995 purified
19	Rat (Wistar)	14d 1x/d (G)	Renal		100	(increased urinary sodium, potassium, chloride, and protein levels; increased serum LDH and HBDH activities)			Santa Maria et al. 1986 analytical grade

Table 3-1 Levels of Significant Exposure to Atrazine - 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
20	Rat (Wistar)	7 or 14d 1x/d (G)	Hepatic		100	(increased serum lipids, AP, and ALT)			Santa Maria et al. 1987 analytical grade
			Bd Wt		100	(25% decrease in body weight)			
21	Rat (Fischer- 344)	7d 1x/d (GO)	Endocr		120 M	(increased pituitary weight)			Simic et al. 1994 >99% pure
			Bd Wt				120 F	(45% decreased body weight gain)	
22	Rat (Wistar)	ppd 1-4 2x/d (G)	Endocr	12.5 F	25 F	(decreased prolactin release in response to pup suckling)			Stoker et al. 1999 98% pure
23	Rabbit (New Zealand)	Gd 7-19 (GW)	Bd Wt	1[c]	5	(slight decrease in maternal body weight gain)	75	(severe maternal weight loss)	Infurna et al. 1988 Aatrex
	Neurological								
24	Rat (Fischer- 344)	12d every 48hr (GO)			120	(developmental neurobehavioral changes)			Peruzovic et al. 1995 purified
25	Rat (Wistar)	1x (GW)					100	(alteration of nerve stimulus conduction)	Podda et al. 1997 NS
	Reproductive								
26	Rat (Long-Evans)	1 or 3d (GW)		150	300	(altered estrus cyclicity)			Cooper et al. 2000 97.1% pure

Table 3-1 Levels of Significant Exposure to Atrazine - 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
27	Rat (Holtzman)	Gd 1-8 (GW)		50			100	(increased percent postimplantation loss, and decreased serum progesterone and serum LH)	Cummings et al. 2000b 97.1% pure
28	Rat (Sprague-Dawley)	Gd 1-8 (GW)		200					Cummings et al. 2000b 97.1% pure
29	Rat (Long-Evans)	Gd 1-8 (GW)		200					Cummings et al. 2000b 97.1% pure
30	Rat (Fischer- 344)	Gd 1-8 (GW)		50			100	(increased percent preimplantation loss; decreased uterine weights)	Cummings et al. 2000b 97.1% pure
31	Rat (Fischer- 344)	12d every 48hr (GO)		120					Peruzovic et al. 1995 purified
32	Rat (Fischer- 344)	7d 1x/d (GO)					120 F	(reduced fecundity)	Simic et al. 1994 >99% pure
33	Rat (Fischer- 344)	7d 1x/d (GO)			120	(altered ovarian/estrus cyclicity)			Simic et al. 1994 >99% pure
	Developmental								
34	Rat (Sprague-Dawley)	Gd 6-15 1x/d (GW)		10	70	(incomplete ossification of skull, hyoid bone, teeth, forepaw metacarpals, and hindpaw distal phalanges)	700	(increased postimplantation loss/litter)	Infurna et al. 1988 Aatrex

Table 3-1 Levels of Significant Exposure to Atrazine - 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
35	Rat (Fischer- 344)	12d every 48hr (GO)			120 (neurobehavioral changes)		Peruzovic et al. 1995 purified
36	Rat (Wistar)	ppd 1-4, 6-9, or 11-14 2x/d (G)		12.5 M	25 M (increased inflammation of lateral prostate, myeloperoxidase levels, and total DNA in prostate of male offspring)		Stoker et al. 1999 98% pure
37	Rabbit (New Zealand)	Gd 7-19 (GW)		5		75 (postimplantation losses, decreased fetal body weight, nonossification of forepaw metacarpals and middle phalanges, hindpaw talus and middle phalanges, and patella)	Infurna et al. 1988 Aatrex
	INTERMEDIATE EXPOSURE						
	Systemic						
38	Rat (Fischer- 344)	28d 1x/d (GW)	Hepatic	50			Aso et al. 2000 98.7% pure
			Renal	50			
			Endocr	50			
			Bd Wt	50			

Table 3-1 Levels of Significant Exposure to Atrazine - 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
39	Rat (Sprague-Dawley)	28d 1x/d (GW)	Hepatic	5	50	(increased relative liver weight)			Aso et al. 2000 98.7% pure
			Renal	50					
			Endocr	50					
			Bd Wt	50					
40	Rat (Donryu)	28d 1x/d (GW)	Hepatic	5	50	(increased relative liver weight)			Aso et al. 2000 98.7% pure
			Renal	50					
			Endocr	50					
			Bd Wt	50					
41	Rat (Wistar)	6 or 12 mo 5 d/wk (F)	Bd Wt				2.7	(30% decreased body weight gain)	Cantemir et al. 1997 96% pure
42	Rat (Long-Evans)	21d 1x/d (GW)	Bd Wt	150	300	(about 10% decrease in body weight gain)			Cooper et al. 1996b >97.1% pure
43	Rat (Sprague-Dawley)	21d 1x/d (GW)	Bd Wt	300					Cooper et al. 1996b >97.1% pure

Table 3-1 Levels of Significant Exposure to Atrazine - 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
44	Rat (Long-Evans)	21d 1x/d (GW)	Endocr		75	(decreased serum LH; increased pituitary prolactin)	Cooper et al. 2000 97.1% pure
			Bd Wt	150	300	(decreased body weight gain)	
45	Rat (Sprague-Dawley)	21d 1x/d (GW)	Endocr		75	(increased pituitary prolactin)	Cooper et al. 2000 97.1% pure
			Bd Wt	150	300	(decreased body weight gain)	
46	Rat CFY	3mo (F)	Hemato	75			Desi 1983 technical purity
			Hepatic	75			
			Renal	38	75	(increased kidney weight)	
			Bd Wt		38	(decreased body weight gain)	
47	Rat (Sprague-Dawley)	14-23d 1x/d (GW)	Endocr		100	(increased adrenal weights; plasma estradiol levels decreased by 61%)	Eldridge et al. 1994a >96% pure
			Bd Wt		100	(body weight decreased by 16%)	
48	Rat (Fischer- 344)	14-23d 1x/d (GW)	Endocr		100	(increased adrenal weights)	Eldridge et al. 1994a >96% pure
			Bd Wt	100			

Table 3-1 Levels of Significant Exposure to Atrazine - 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
49	Rat (Sprague-Dawley)	1x/d pnd 22-48 (GO)	Endocr		50 M (reduced serum and intratesticular testosterone levels)		Friedmann 2002
50	Rat (Wistar)	20d (ppd 22-41) (GW)	Hepatic	100	200 (decreased absolute and increased relative liver weights)		Laws et al. 2000 97.1% pure
			Renal	100	200 (decreased absolute and relative kidney weights)		
			Endocr		12.5 (decreased absolute and relative pituitary weight)		
			Bd Wt	100	200 (16% decrease in body weight gain)		
51	Rat (Sprague-Dawley)	1 x/d pnd 22-27 (G)	Endocr	50 M	100 M (reduced serum and interstitial fluid testosterone concentrations)		Trentacoste et al. 2001
			Bd Wt		100 M (9% decrease in weight gain)		
52	Rat (Fischer- 344)	1, 3, or 9 mo (F)	Endocr	45.2			Wetzel et al. 1994 97% pure
			Bd Wt		22.6 (body weight gain decreased by 11%)		
53	Rat (Sprague-Dawley)	1, 3, or 9 mo (F)	Endocr		6.9 (increased plasma estradiol levels)		Wetzel et al. 1994 97% pure
			Bd Wt		39.2 (body weight gain decreased by 15%)		

Table 3-1 Levels of Significant Exposure to Atrazine - 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
54	Pig (Landrace)	19d (F)	Resp	2			Curic et al. 1999 >99% pure
			Cardio		2	(degeneration of a small number of myocardial fibers)	
			Hepatic		2	(mild degeneration and inflammation and mild chronic interstitial hepatitis)	
			Renal		2	(subacute glomerulitis; degeneration and desquamation of proximal tubules)	
			Endocr	2			
55	Pig landrace	19d (F)	Hepatic		2	(350% increase in serum gamma-glutamyltransferase; mild liver histological changes)	Gojmerac et al. 1995 99% pure
	Immuno/ Lymphoret						
56	Rat (Wistar)	3wk (F)			15.4 M	(lymphopenia)	Vos and Krajnc 1983 97% pure
57	Pig (Landrace)	19d (F)			2	(lymphoid depletion in lymph nodes and spleen)	Curic et al. 1999 >99% pure
	Neurological						
58	Rat CFY	3mo (F)		75			Desi 1983 technical purity
	Reproductive						
59	Rat (Sprague-Dawley)	28d 1x/d (GW)		50			Aso et al. 2000 98.7% pure

Table 3-1 Levels of Significant Exposure to Atrazine - 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
60	Rat (Fischer- 344)	28d 1x/d (GW)		50				Aso et al. 2000 98.7% pure
61	Rat (Donryu)	28d 1x/d (GW)		50				Aso et al. 2000 98.7% pure
62	Rat (Long-Evans)	21d 1x/d (GW)		75	150	(disrupted estrus cycle; altered serum estradiol and progesterone levels)		Cooper et al. 1996b >97.1% pure
63	Rat (Sprague-Dawley)	21d 1x/d (GW)		75	150	(altered estrus cyclicity; elevated serum progesterone; pseudopregnancy)		Cooper et al. 1996b >97.1% pure
64	Rat (Sprague-Dawley)	14-23d 1x/d (GW)			100	(decreased ovarian weights; decreased plasma estradiol levels)		Eldridge et al. 1994a >96% pure
65	Rat (Fischer- 344)	14-23d 1x/d (GW)			100	(decreased ovarian and uterine weights)		Eldridge et al. 1994a >96% pure
66	Rat (Fischer- 344)	14-23d 1x/d (GW)			300	(altered estrus cyclicity)		Eldridge et al. 1994a >96% pure
67	Rat (Sprague-Dawley)	14-23d 1x/d (GW)			100	(altered estrus cyclicity)		Eldridge et al. 1994a >96% pure

Table 3-1 Levels of Significant Exposure to Atrazine - 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
68	Rat (Sprague-Dawley)	45d 1x/d (GW)		5	40 (abnormal estrus cycle)		Eldridge et al. 1999a 97.1% pure
69	Rat (Sprague-Dawley)	26w 1x/d (F)		4.6	33 (abnormal estrus cycle)		Eldridge et al. 1999a 97.1% pure
70	Rat (Charles River)	2 gen (F)		26.7			EPA 1987e technical--% NS
71	Rat (Sprague-Dawley)	1, 3, or 9 mo (F)			6.9 (increased length of estrus)		Wetzel et al. 1994 97% pure
72	Pig (Landrace)	19d (F)			2 (disruption of estrus cyclicity; ovarian cysts)		Curic et al. 1999 >99% pure
73	Pig landrace	19d (F)			2 (disrupted estrogen and progesterone levels; disruption of estrus cyclicity; ovarian histopathology)		Gojmerac et al. 1996 99% pure
74	Pig Swedish Landrace x Large	19d (F)			1[d] (short-term delay in estrus onset)		Gojmerac et al. 1999 NS

Table 3-1 Levels of Significant Exposure to Atrazine - 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
	Developmental						
75	Rat (Wistar)	1 x/d 22 d pnd 21-43 (G)			100 F (reduced uterine weights; delayed vaginal opening)		Ashby et al. 2002
76	Rat Charles River)	2 gen (F)		30.9			EPA 1987e technical--% NS
77	Rat (Wistar)	20d (ppd 22-41) (GW)		25	50 (delayed vaginal opening)		Laws et al. 2000 97.1% pure
78	Rat (Wistar)	31d 1x/d (GW)			12.5 (delayed preputial separation)		Stoker et al. 2000 97.1% pure
	CHRONIC EXPOSURE						
	Death						
79	Rat (Sprague-Dawley)	12, 15, 18, or 24 mo (F)				31.9 (15% increase in mortality)	Wetzel et al. 1994 97% pure
80	Mouse (CD-1)	daily 91wks (F)				482.7 F (decreased survival)	EPA 1987b technical
81	Dog (Beagle)	52wk (F)				33.8 F (death in 1/6 dogs)	EPA 1987f technical

Table 3-1 Levels of Significant Exposure to Atrazine - 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
	Systemic						
82	Rat (CD)	12mo (F)	Resp	52			EPA 1984f, 1987d technical--% NS
			Cardio	52			
			Gastro	52			
			Hemato	34.6 F	70.6 F (decreased RBC, hemoglobin, hematocrit; increased platelet, leukocyte, mean corpuscular hemoglobin)		
			Musc/skel	52			
			Hepatic	25.5 M	52 M (decreased liver weight, total triglyceride, globulin; increased albumin/globulin ratio)		
			Renal	25.5 M	52 M (decreased kidney weight, specific gravity; increased urine volume, pelvic calculi)		
			Endocr	25.5 M	70.6 F (increased adrenal gland weight; enlarged pituitaries)		
			Dermal	52 M			
			Ocular	52 M			
			Bd Wt	3.5 M	25 (decreased body weight)		
			Metab	25.5 M	52 (decreased serum glucose, calcium)		
83	Rat (Charles River)	2 gen (F)	Bd Wt	2.4	26.7 (10-15% decrease in body weight gain)		EPA 1987e technical--% NS

Table 3-1 Levels of Significant Exposure to Atrazine - 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
84	Rat (Fischer- 344)	126wk (F)	Bd Wt		58 M (10% decrease in body weight gain)		Pinter et al. 1990 98.9% pure
85	Rat (Fischer- 344)	12, 15, 18, or 24 mo (F)	Endocr	45.2			Wetzel et al. 1994 97% pure
86	Rat (Sprague-Dawley)	12, 15, 18, or 24 mo (F)	Endocr	39.2			Wetzel et al. 1994 97% pure
87	Mouse (CD-1)	daily 91wks (F)	Cardio			385.7 M (increased incidence of cardiac thrombi) 246.9[b] F (increased incidence of cardiac thrombi)	EPA 1987b technical
			Hemato		194[b] M (reductions in mean erythroid parameters)		
					482.7 F (reductions in mean erythroid parameters)		
			Renal		482.7 F (slight decrease in mean absolute kidney weight)		
			Ocular	385.7[b] M			
				482.7 F			

Table 3-1 Levels of Significant Exposure to Atrazine - 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
88	Dog (Beagle)	52wk (F)	Resp	33.8			EPA 1987f technical
			Cardio	4.97		33.65 (electrocardiographic changes; atrial dilatation; fluid-filled pericardium; enlarged heart; atrophy of atrial myocardium; edema)	
			Gastro	33.8			
			Hemato	4.97	33.65 (decreased RBC, hemoglobin, and hematocrit; increased platelet counts)		
			Musc/skel	33.8			
			Hepatic	4.97	33.65 M (increased relative liver weight; increased liver to brain weight)		
			Renal	33.8			
			Endocr	33.8			
			Dermal	33.8			
			Ocular	33.8			
			Bd Wt	4.97	33.65 M (body weight decreased by 19%)		
	Reproductive						
89	Rat (Fischer- 344)	12, 15, 18, or 24 mo (F)		45.2			Wetzel et al. 1994 97% pure

Table 3-1 Levels of Significant Exposure to Atrazine - 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
90	Rat (Sprague-Dawley)	12, 15, 18, or 24 mo (F)			5.6 (increased length of estrus after 18 months)		Wetzel et al. 1994 97% pure
	Cancer						
91	Rat (Fischer- 344)	126wk (F)				58 M[b] (CEL: increased number of rats with malignant tumors) 65 F (CEL: increased incidence of uterine adenocarcinoma and leukemia/lymphoma; increased number of rats with malignant tumors)	Pinter et al. 1990 98.9% pure
92	Rat (Sprague-Dawley)	24 mo (F)				31.9 (CEL: increased incidence of mammary and pituitary tumors at 1 year)	Wetzel et al. 1994 97% pure

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

b Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c Used to derive an acute-duration minimal risk level (MRL) of 0.01 mg/kg/day; based on a NOAEL of 1 mg/kg/day for decreased body weight gain in pregnant rabbits exposed to atrazine on gestational days 7-19 (Infurna et al. 1988), and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

d Used to derive an intermediate-duration minimal risk level (MRL) of 0.003 mg/kg/day; based on a LOAEL of 1 mg/kg/day for delayed estrus onset (Gojmerac et al. 1999), and divided by an uncertainty factor of 300 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 3 for human variability).

ALT = alanine aminotransferase; AP = alkaline phosphatase; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); DNA = deoxyribonucleic acid; Endocr - endocrine; (F) = feed; F = female; (G) = gavage; gastro = gastrointestinal; gd = gestation day; gen = generation; (GO) = gavage in oil; (GW) = gavage in water; HBDH = hydroxybutyrate dehydrogenase; Hemato = hematological; hr = hour(s); LD50 = lethal dose, 50% kill; LDH = lactate dehydrogenase; LH = luteinizing hormone; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; mg /kg/day = milligram per kilogram per day; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; ppd = post-parturition day; RBC = red blood cell(s); Resp = respiratory; wk = week(s); x = times

Figure 3-1. Levels of Significant Exposure to Atrazine - Oral

Acute (≤14 days)

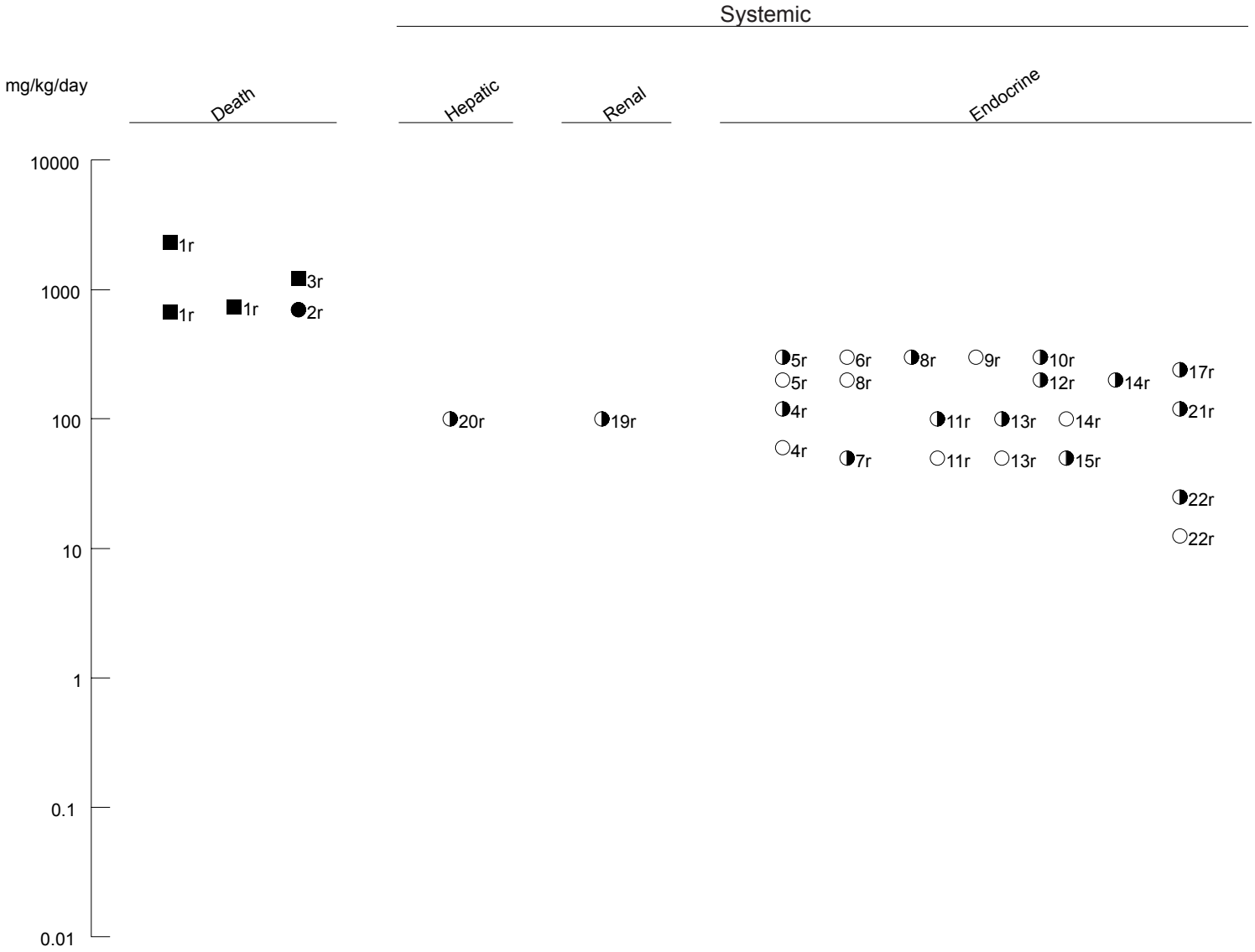


Figure 3-1. Levels of Significant Exposure to Atrazine - Oral (*Continued*)

Acute (≤14 days)

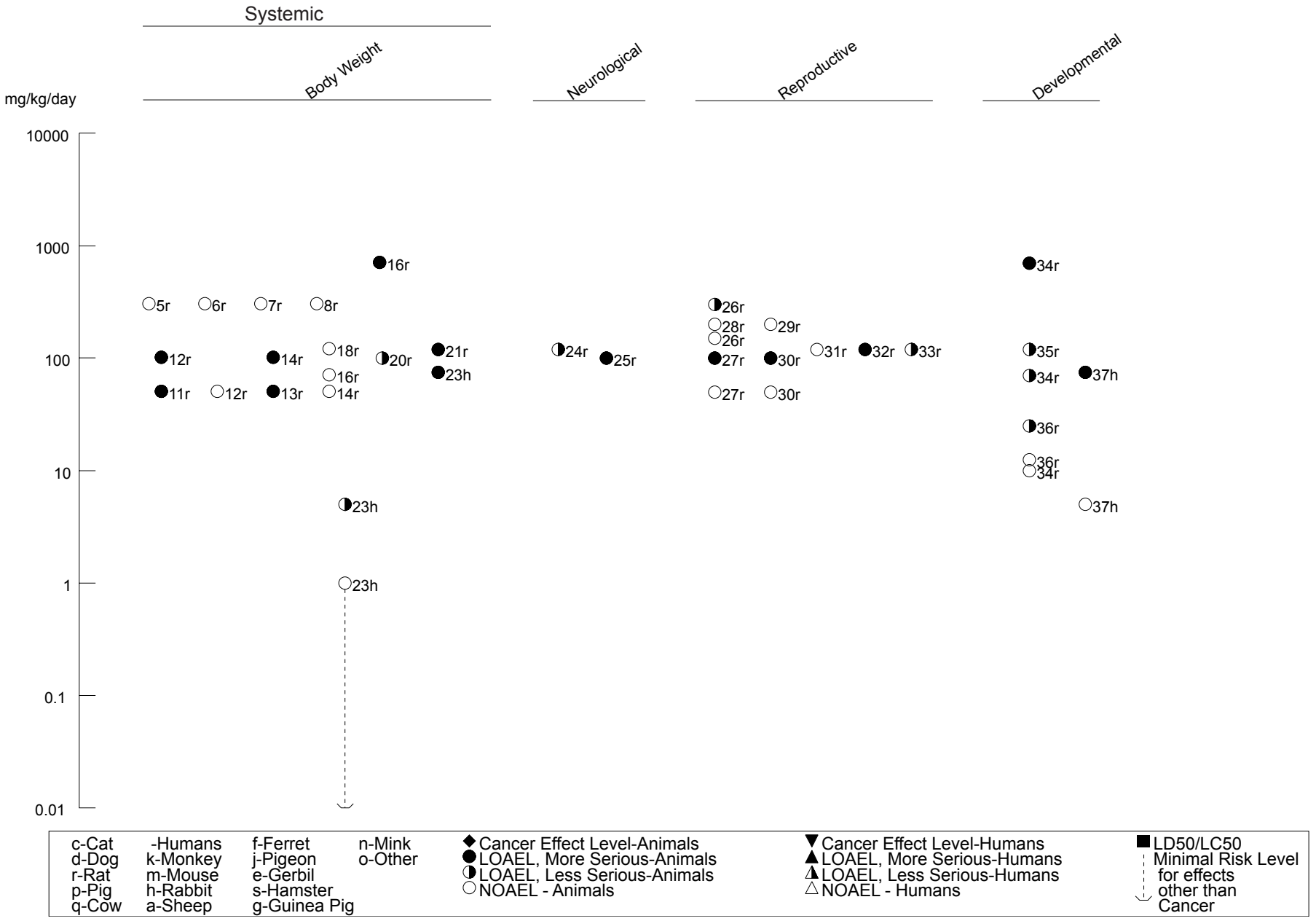


Figure 3-1. Levels of Significant Exposure to Atrazine - Oral (*Continued*)

Intermediate (15-364 days)

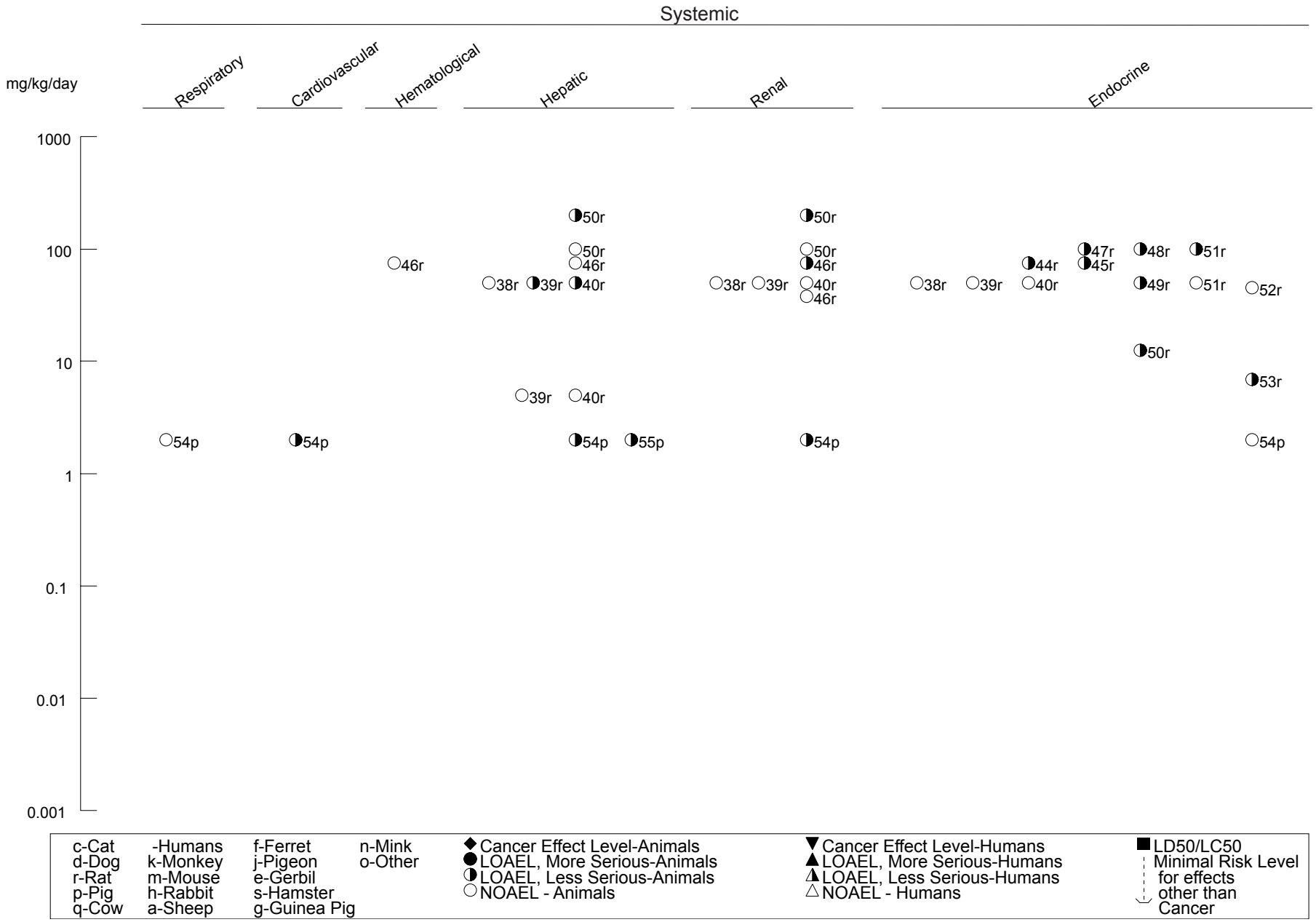


Figure 3-1. Levels of Significant Exposure to Atrazine - Oral (*Continued*)

Intermediate (15-364 days)

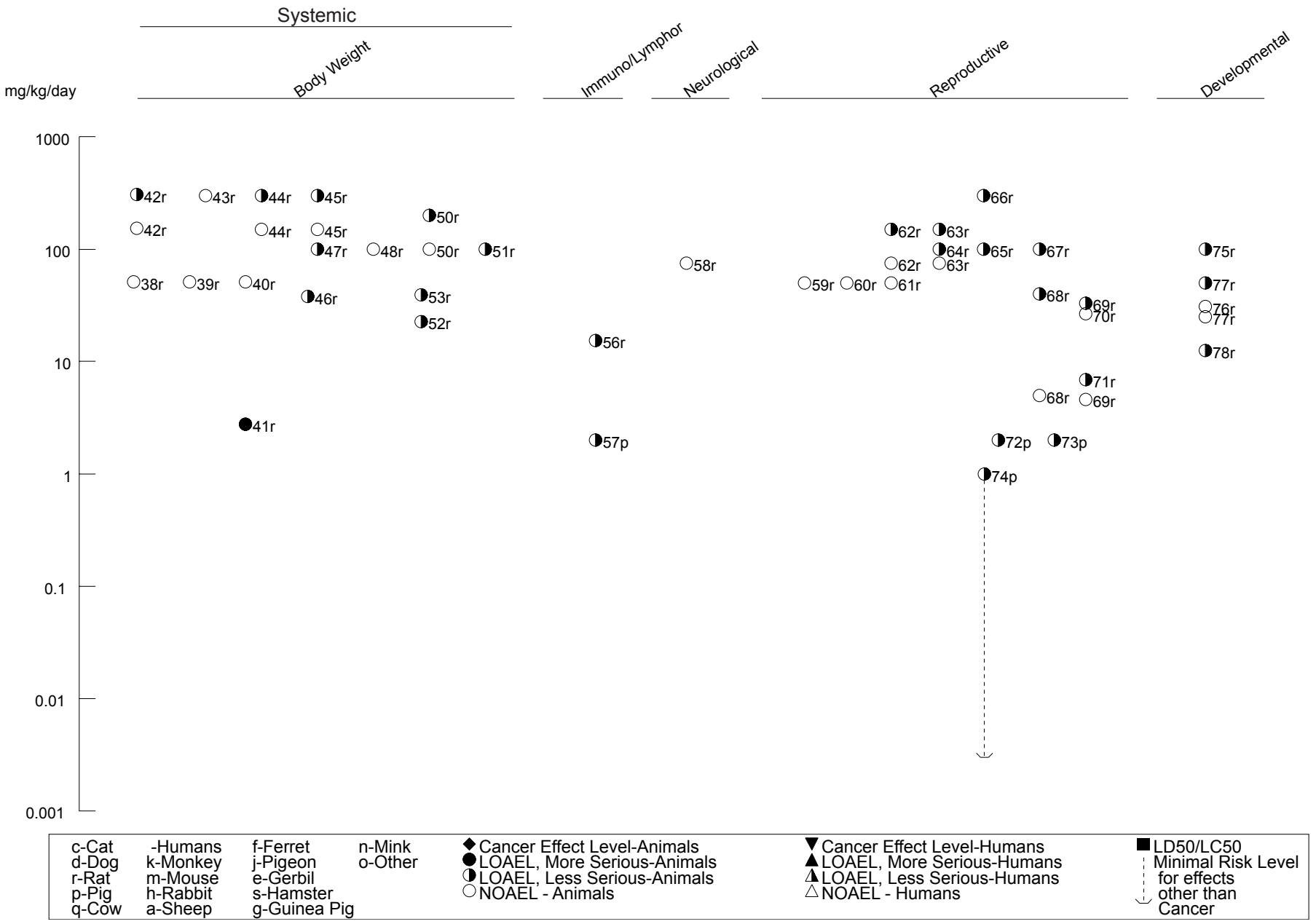
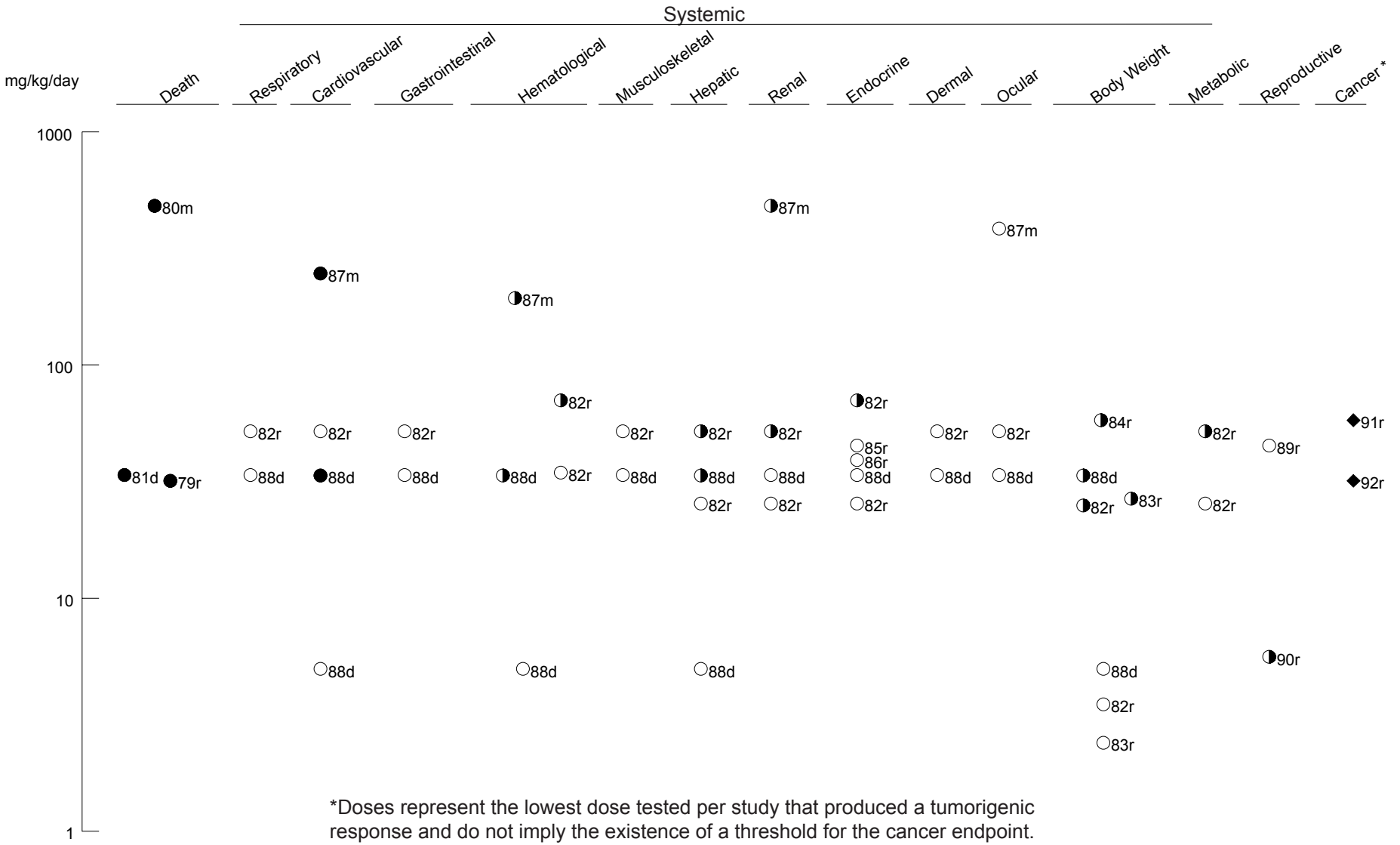


Figure 3-1. Levels of Significant Exposure to Atrazine - Oral (*Continued*)

Chronic (≥365 days)



1999); no clinical manifestations were apparent. Female and male mice exposed to atrazine in the diet at ≥247 and 386 mg/kg/day, respectively, had an increased incidence of cardiac thrombi (EPA 1987b). In contrast, no histopathological alterations were observed in male and female rats exposed to up to 52 and 71 mg/kg/day atrazine, respectively, in the diet for 12–24 months (EPA 1984f, 1986, 1987d) or in sheep consuming hay sprayed with atrazine (approximately 47 mg atrazine/kg body weight/day) for 27 days (Johnson et al. 1972).

Gastrointestinal Effects. No histological alterations were observed in the gastrointestinal tracts of rats exposed to 52–71 mg/kg/day for 12–24 months (EPA 1984f, 1986, 1987d) or in sheep exposed to approximately 47 mg atrazine/kg body weight/day for 25 days (Johnson et al. 1972).

Hematological Effects. Although some animal studies have reported hematological effects, the results have been inconsistent across studies. Decreases in erythrocyte, hemoglobin, and hematocrit levels and increases in mean platelet levels were observed in female rats exposed to 71 mg/kg/day atrazine in the diet for 12–24 months (EPA 1984f, 1986, 1987d). No effects were observed in female rats exposed to 35 mg/kg/day or in male rats exposed to doses up to 52 mg/kg/day. Decreases in erythrocyte and hemoglobin levels and increases in platelet counts were also seen in dogs exposed to about 34 mg/kg/day atrazine for 52 weeks (EPA 1987f); however, the study authors considered these changes to be secondary to decreased body weight. Reductions in mean erythroid parameters were noted in mice administered atrazine in the diet at >194 mg/kg/day (males) or 483 mg/kg/day (females); these alterations, however, did not correlate with any other hematological changes, and the authors suggest that they were secondarily related to decreased body weight and/or food and water consumption (EPA 1987b). No alterations in erythrocyte or platelet parameters were observed in rats exposed to 75 mg/kg/day atrazine in the diet for 3 months (Dési 1983), rats exposed to 9.8–43.1 mg/kg/day atrazine in the diet for 6 months (Suschetet et al. 1974), or sheep exposed to approximately 47 mg/kg/day atrazine in the diet for 25 days (Johnson et al. 1972).

A decrease in total white blood cell counts was observed in male and female rats exposed to 43 and 10 mg/kg/day atrazine, respectively, in the diet for 6 months; white blood cell levels were increased in female rats exposed to 71 mg/kg/day atrazine in the diet for 12 months (EPA 1984f, 1987d). No alterations in white blood cell levels were observed in male rats exposed to 52 mg/kg/day for 12 months (EPA 1984f, 1987d) or in sheep consuming hay sprayed with atrazine for 25 days (Johnson et al. 1972).

Musculoskeletal Effects. No histopathological changes were noted in skeletal muscle of male or female rats exposed to up to 52 or 71 mg/kg/day atrazine, respectively, in the diet for 12 months (EPA 1984f, 1986, 1987d) or dogs exposed to up to 34 mg/kg/day atrazine in the diet for 52 weeks (EPA 1987f).

Hepatic Effects. The available data suggest that the liver is a target of atrazine toxicity with apparent species differences in sensitivity and, therefore, in the extent of damage. Of the tested animal species, the pig appears to be the most sensitive species. Intermediate-duration exposure of pigs to 2 mg/kg/day resulted in a 350% increase in serum γ-glutamyltransferase activity and mild histopathological changes, including chronic interstitial inflammation, lymphocyte and eosinophil infiltration, and narrowing and irregular forms of bile canaliculi (Gojmerac et al. 1995). Ćurić et al. (1999) found similar histopathological changes in the livers of pigs exposed to 2 mg/kg/day for 19 days.

Alterations in clinical chemistry parameters and liver weight have been observed in rats, although strain differences have been observed. In Wistar rats receiving gavage doses of atrazine in gum arabic for up to 14 days (Santa Maria et al. 1987), dose-related increases in serum total lipids, alkaline phosphatase activity, and alanine aminotransferase activity were observed at 100 mg/kg/day. Decreases in serum glucose levels and subcellular changes including proliferation and degeneration of the smooth endoplasmic reticulum, lipid accumulation, mitochondrial malformation, and alteration of bile canaliculi were observed at 200 mg/kg/day. Significantly decreased relative liver weight was observed at 400 mg/kg/day; the decreased relative liver weight may be reflective of the decreased body weight also observed in these animals. Significant decreases in serum glucose, calcium, total triglyceride, and globulin (males only) levels, and an increase in albumin/globulin ratios (males only) were observed in male and female CD rats exposed to 52 or 71 mg/kg/day, respectively, in the diet for 12–24 months (EPA 1984f, 1986, 1987d). Significantly decreased liver weight and liver/brain weight ratio were also observed in males at 12 months); no hepatic effects were observed at 26 and 35 mg/kg/day for males and females, respectively (EPA 1984f, 1986, 1987d). Liver effects (increased relative liver weights) have also been observed in Sprague-Dawley and Donryu rats receiving gavage dose of 50 mg/kg/day, but not 5 mg/kg/day, for 28 days (Aso et al. 2000); no histological alterations were observed. No liver effects were observed in similarly exposed F344 rats (Aso et al. 2000). An increase in relative liver weight was also observed in male dogs exposed to 34 mg/kg/day atrazine in the diet for 52 weeks; no alterations in clinical chemistry parameters were observed. This study identified a NOAEL of 5 mg/kg/day. No liver effects were observed in mice receiving a single dose of up to 875 mg/kg atrazine (as the commercial

product Aatrex) (Fournier et al. 1992) or sheep exposed to 47 mg/kg/day atrazine in the diet for 25 days (Johnson et al. 1972).

Renal Effects. Kidney effects have been observed in rats and pigs, but not in mice, sheep, or dogs. In male Wistar rats administered atrazine via gavage at 100 mg/kg/day or higher for 14 days, increases in urinary sodium, potassium, chloride, and protein levels, and serum lactate dehydrogenase and γ-hydroxybutyrate dehydrogenase activities (considered by the study authors to be of renal, not hepatic, origin) were observed (Santa Maria et al. 1986); this study did not identify a NOAEL. Exposure of male rats to 52 mg/kg/day atrazine in the diet for 12 months resulted in decreased kidney weight and kidney to brain weight ratios, decreased specific gravity and increased volume of urine, and increased incidence of pelvic calculi in the kidney; females exposed to 71 mg/kg/day had only increased relative kidney weight (EPA 1984f, 1986, 1987d). In this study, no renal effects were observed at 26 (males) or 35 (females) mg/kg/day. No significant alterations in kidney weight, gross pathology, or histopathology were observed in female Sprague-Dawley, F344, and Donryu rats gavaged with up to 50 mg/kg/day for 28 days (Aso et al. 2000). The rat data suggest that males may be more sensitive to the renal toxicity of atrazine than females.

Subacute glomerulitis and degeneration and desquamation of the proximal tubules were observed in female pigs receiving 2 mg/kg/day atrazine in the diet for 19 days (Ćurić et al. 1999). Female mice administered atrazine in the diet at 483 mg/kg/day for ≥91 weeks had a slight, but statistically significant, decrease in mean absolute kidney weight; however, the authors indicate that this did not correlate with any significant gross or microscopic pathology (EPA 1987b). No renal effects were observed in mice administered single gavage doses of up to 875 mg/kg/day atrazine (kidney weight and gross pathology examined) (Fournier et al. 1992), in sheep receiving gavage doses of 50 mg/kg/day for 28 days (gross and histopathology examined) (Johnson et al. 1972), or in dogs administered up to 71 mg/kg/day atrazine in the diet for 52 weeks (gross and histopathology examined) (EPA 1987f).

Endocrine Effects. Several mild to moderate endocrine effects have been observed in laboratory animals following atrazine administration, the majority of which are related to reproductive effects (see Section 3.2.2.5). The endocrine effects consisted of alterations in gland weight, histological damage in some endocrine glands, and alterations in hormone levels. A number of studies have found pituitary effects. Increased pituitary weight, hyperemia and hypertrophy, and impaired testosterone metabolism were observed in male Fischer rats administered 12 mg/kg/day atrazine by gavage for 7 days (Babic-Gojmerac et al. 1989). The levels of three testosterone metabolites (5α-androstane-3α,17β-diol,

5α-dihydrotestosterone, and androstene-3,17-dione) were decreased in the anterior pituitary, suggesting impaired metabolism of testosterone. No effects on the pituitary gland were observed at 6 mg/kg/day (Babic-Gomerac et al. 1989). Atrazine exposures of 50 mg/kg/day administered by gavage for 3 days significantly reduced serum ($p<0.008$) and intratesticular ($p<0.005$) levels of testosterone in juvenile male Sprague-Dawley rats. Given the same dose for 27 days, serum and testicular levels of testosterone were also significantly reduced ($p<0.0002$ and $p<0.0003$, respectively) (Friedmann 2002). Peripubertal Sprague-Dawley rats administered atrazine by gavage from postnatal day 22 to 47 at doses of 100 and 200 mg/kg/day had significantly reduced ($p<0.05$) serum and interstitial fluid testosterone concentrations (Trentacoste et al. 2001). A decrease in body weight gain was also observed in these rats. To assess whether the alterations in testosterone were directly related to atrazine or were secondary to the decreased food intake. Vehicle-gavaged rats were fed amounts of feed equivalent to that consumed by the atrazine-exposed rats. Decreases in serum testosterone concentration, androgen-dependent organ weights, and serum luteinizing hormone levels were found in the food-restricted controls.

Increased pituitary weights were observed in male rats gavaged with 120 mg/kg/day for 7 days, and then were observed for 14 days (Šimić et al. 1994). Female CD rats exposed to 71 mg/kg/day atrazine in the diet for 12 months had an increased incidence of enlarged pituitaries (EPA 1984f, 1987d). No pituitary effects were observed in the male rats. No histological alterations were observed in the pituitary of dogs exposed to 34 mg/kg/day atrazine in the diet for 52 weeks (EPA 1987f).

Possibly related to the effects on the pituitary are alterations in a number of pituitary-related and controlled hormones. Ovariectomized Long-Evans rats implanted with estrogen-filled silastic capsules (which standardizes the estrogen levels and eliminates the ovary's influence on the pituitary) and administered 50 mg/kg/day atrazine or higher for 3 days had increased levels of pituitary prolactin and decreased serum prolactin levels (Cooper et al. 2000). The decrease in serum prolactin levels was also observed in similarly treated Long-Evan rats administered a single dose of 300 mg/kg/day (Cooper et al. 2000). In parallel studies, Sprague-Dawley rats treated in an identical manner and administered 300 mg/kg/day for 3 days had no increases in pituitary prolactin levels, but did have decreased serum prolactin levels (Cooper et al. 2000); a single dose of 300 mg/kg/day did not result in alterations in prolactin levels. Long-Evans and Sprague-Dawley rats treated similarly with 75–300 mg/kg/day for 21 days had increased pituitary prolactin, and the Long-Evans rats also had decreased serum luteinizing hormone and prolactin (Cooper et al. 2000). A significant increase in serum prolactin levels was observed in Sprague-Dawley rats exposed to 39 mg/kg/day atrazine in the diet for 9 months, but no alterations were observed after 12, 18, or 24 months of exposure (Wetzel et al. 1994). No alterations in

serum prolactin levels were observed in female F344 similarly exposed to up to 45 mg/kg/day for 24 months (Wetzel et al. 1994). Wistar rat dams that received 25 mg/kg/day atrazine on lactation days 1–4 had decreased prolactin release in response to pup suckling (Stoker et al. 1999).

In the studies of ovariectomized rats supplemented with estrogen (via an implanted silastic capsule), decreases in serum luteinizing hormone levels were observed at 300 mg/kg/day in Long Evans rats receiving a single dose (Cooper et al. 2000), 50 mg/kg/day in Long Evans rats receiving daily doses for 3 days (Cooper et al. 2000), 75 mg/kg/day in Long Evans rats receiving 21 doses of atrazine (Cooper et al. 2000), and 150 mg/kg/day in Sprague-Dawley rats exposed to atrazine for 21 days (Cooper et al. 2000). In ovariectomized Long Evans rats supplemented with estrogen and gonadotropin releasing hormone, a 3-day exposure to atrazine resulted in higher blood luteinizing hormone levels than in atrazine-exposed rats not receiving gonadotropin releasing hormone (Cooper et al. 2000), suggesting that atrazine disrupts neuroendocrine regulation.

The alterations in pituitary hormones result in changes in peripheral gland hormone levels. As discussed in the Reproductive Effects section, significant increases and decreases in plasma estradiol and progesterone levels have been observed in rats following acute, intermediate, or chronic duration exposure to atrazine (Cooper et al. 1996b; Cummings et al. 2000b; Eldridge et al. 1994a; Wetzel et al. 1994).

Several studies have examined the adrenal glands following oral exposure to atrazine, and most studies did not find adverse effects. No alterations in adrenal weight and/or histopathology were observed in mice receiving a single gavage dose of 875 mg/kg/day (Fournier et al. 1992), Sprague-Dawley, F344, and Donryu rats administered 50 mg/kg/day for 28 days (Aso et al. 2000), F0, F1, and F2 albino rats exposed to up to 31 mg/kg/day atrazine in the diet (EPA 1987e), sheep exposed to up to 47 mg/kg/day atrazine for 25 days in the diet (Johnson et al. 1972), pigs that received 2 mg/kg/day in the diet for 19 days (Ćurić et al. 1999), or dogs exposed to 34 mg/kg/day atrazine in the diet for 52 weeks (EPA 1987f). Increases in adrenal weights were observed in female Sprague-Dawley and F344 rats administered by gavage 100 mg/kg/day atrazine (Eldridge et al. 1994a) and in female rats, but not males, exposed to 71 mg/kg/day atrazine in the diet for 12 months (EPA 1984f, 1987d).

The thyroid may also be a target of atrazine toxicity. It is not known whether the thyroid changes are direct results of atrazine toxicity or indirect results via atrazine effects on the regulation of pituitary hormones. A significant increase in relative thyroid weight was reported in Wistar rats dosed with

139 mg/kg/day atrazine by gavage for 3 weeks (Vos et al. 1983); because a decrease in body weight gain was also observed at this dosage, it is difficult to determine whether the increased thyroid weight was due to a direct effect of atrazine or was reflective of the decreased body weight. A decrease in serum triiodothyronine levels were observed in rats receiving gavage doses of 240 mg/kg/day atrazine for 6–12 days (Kornilovskaya et al. 1996). Histological damage to thyrocytes (decreased diameter, decreased cell height, increased), increased thyroid follicle size, and desquamation of the epithelium of the follicular cavity were also observed in these rats. No histological effects on the thyroid were reported in rats exposed to 71 mg/kg/day atrazine in the diet for 12 months (EPA 1984f, 1987d) and no alterations in thyroid stimulating hormone levels were observed in Long-Evans and Sprague-Dawley rats receiving gavage doses of atrazine for 1, 3, or 21 days (Cooper et al. 2000). No histopathological changes were seen in the thyroid and no clinical signs were observed in female cross-bred pigs administered 2 mg/kg/day atrazine in the feed for 19 days (Ćurić et al. 1999). There was no alteration in thyroid stimulating hormone levels observed in Wistar rats administered atrazine by gavage for 19 days (postnatal days 22–41) with doses of 0, 50, 100, or 200 mg/kg/day (Laws et al. 2000).

Dermal Effects. Information on the dermal toxicity of atrazine is limited to two studies that found no gross or histological abnormalities in the skin of male and female rats administered up to 52.0 and 71 mg/kg/day technical atrazine, respectively, in the diet for 12–24 months (EPA 1984f, 1986, 1987d) or in dogs that received up to about 34 mg/kg/day technical atrazine in the feed for 52 weeks (EPA 1987f).

Ocular Effects. No treatment-related ocular effects were noted in male and female rats administered up to 52 and 71 mg/kg/day technical atrazine, respectively, in the diet for 12–24 months (EPA 1984f, 1986, 1987d), in male and female mice that received up to 386 and 483 mg/kg/day technical atrazine, respectively, in the diet for ≥91 weeks (EPA 1987b), or in dogs that received up to about 34 mg/kg/day technical atrazine in the feed for 52 weeks (EPA 1987f).

Body Weight Effects. Many rat studies involving acute, intermediate, or chronic exposure to atrazine in the diet or by gavage showed mild to severe weight loss (Cantemir et al. 1997; Cooper et al. 2000; Cummings et al. 2000b; Eldridge et al. 1994a, 1999a; EPA 1984f, 1986, 1987d; Infurna et al. 1988; Peruzović et al. 1995; Pintér et al. 1990; Santa Maria et al. 1987; Šimić et al. 1994; Stevens et al. 1999; Suschetet et al. 1974; Tennant et al. 1994b; Wetzel et al. 1994). Some of these studies noted corresponding reductions in food intake (Infurna et al. 1988; Suschetet et al. 1974), and recovery following cessation of atrazine administration was noted in one study (Peruzović et al. 1995). One study in mice showed no weight loss after a single dose of up to 875 mg/kg (Fournier et al. 1992). Mice

exposed to atrazine in the diet for ≥91 weeks had reduced mean body weight and percent body weight gain at ≥38 mg/kg/day (males) and ≥48 mg/kg/day (females) (EPA 1987b; Stevens et al. 1999). Mean food and water consumption was also decreased in male and female mice at ≥194 and ≥247 mg/kg/day, respectively (EPA 1987b). Rabbits exposed to 75 mg/kg/day atrazine by gavage experienced severe food intake reduction and weight loss (Infurna et al. 1988). A 1-year diet study in dogs showed that terminal body weights were 19 and 14% less than controls in males and females, respectively, exposed to 34 mg/kg/day atrazine and body weight gain was reduced by 17 and 14%, respectively (EPA 1987f). Food intake was also decreased in these dogs by a similar amount as body weight decreased (EPA 1987f).

Metabolic Effects. No studies were located regarding metabolic effects in humans or animals following oral exposure to atrazine.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after oral exposure to atrazine.

Líšková et al. (2000) performed a variety of tests to assess the immunotoxicity of atrazine in Balb/c and C57B1/10 mice. In the plaque-forming cell assay, which tests humoral immunity by determining the integrity of three immune cells, macrophages, T cells, and B cells, administration of 100 mg/kg/day atrazine in corn oil by gavage for 10 days resulted in a 16 and 25% decrease in the number of IgM plaque-forming cells per million splenic cells as compared to saline and oil controls, respectively. Other immunological effects observed in this group of mice included a decrease in spleen cellularity and a decrease in relative thymus weight. No significant alterations were observed in politeal lymph node activation in the graft versus host and host versus graft reactions, which were used to assess the potential of atrazine to induce autoimmune disease, or the delayed-type hypersensitivity reaction. No immunological effects were observed at 20 mg/kg/day.

Female Wistar rats treated with 15 mg/kg/day atrazine for 3 weeks had decreased lymphocyte counts (Vos et al. 1983). Exposure to 139 mg/kg/day also produced increased thyroid and mesenteric lymph node weights and decreased thymus weights (Vos et al. 1983); no increases in histological abnormalities were seen. Lymphoid depletion in the lymphoid follicles of prescapular and mesenteric lymph nodes, accompanied by infiltration of eosinophilic granulocytes, was seen in female cross-bred pigs administered

2 mg/kg/day atrazine in the feed for 19 days (Ćurić et al. 1999). Lymphoid depletion was also seen in the lymph nodes of the white pulp of the spleen.

3.2.2.4 Neurological Effects

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

Sixty and 90 minutes after a single oral dose of 100 mg/kg atrazine was administered to Wistar rats, the spontaneous cerebellar activity (spontaneous firing rate of Purkinje cells) was reduced to 50 and 80%, respectively, of control values (Podda et al. 1997). The evoked spike activity of Purkinje cells following stimulation of the radial nerve was almost completely abolished in atrazine-treated rats, and the amplitude of the cerebellar potentials of N2 (expression of the mossy fibers input) and CF (expression of the climbing fibers input) were reduced by 58 and 75%, respectively, 30 minutes after atrazine administration (Podda et al. 1997). Six days of oral exposure to Ceazine herbicide (used to deliver 220 mg/kg/day atrazine) resulted in decreased brain monoamine oxidase activity in Wistar rats (Bainova et al. 1979). All cerebellar activities recovered fully in 1.5–2 hours. Rats treated with up to 75 mg/kg/day atrazine in the diet for 3 months showed no differences from controls in running time to the goal (food) or number of errors in behavioral maze studies (Dési 1983).

3.2.2.5 Reproductive Effects

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

Much of the research on the reproductive toxicity of atrazine has focused on the disruption of the endocrine system and its effect on estrus cyclicity. Peruzović et al. (1995) monitored estrus cyclicity in F344 rats before, during, and after atrazine exposure, which consisted of gavage administration of 120 mg/kg atrazine (purified by recrystallization) every 48 hours for a total of 6 doses. Atrazine exposure did not affect duration or frequency distribution of the individual phases of estrus. In contrast, F344 rats exposed to 120 mg/kg/day for 7 consecutive days showed a significant decrease in the percent of females with regular ovarian cycling, an increase in the average length of diestrus (10.5 days compared to 2 days in controls), and an increase in the average number of days between treatment cessation and the first proestrus (6.2 days compared to 2.2 days in controls) (Šimić et al. 1994). Gavage dosing of 300 mg/kg/day for 3 days resulted in pseudopregnancy (defined as maintaining diestrus for ≥12 days and

having elevated serum progesterone levels) in Long Evans rats; this dose also blocked the appearance of subsequent proestrus and ovulation (Cooper et al. 2000). No effect on estrus cyclicity was observed at 150 mg/kg/day. The acute data suggest that both dose and duration of exposure may be important in the atrazine-induced disruption of the estrus cycle in rats.

The intermediate-duration studies that examined atrazine-induced alterations in the estrus cycle support the findings of the acute-duration studies that the threshold of toxicity appears to be dose- and duration-related; the rat data also suggest strain differences. No statistically significant alterations in estrus cycle were observed in Sprague-Dawley, F344, or Donryu rats administered via gavage 50 mg/kg/day atrazine for 28 days (Aso et al. 2000). This study has low statistical power because of the small number of animals tested (6/group/strain). Persistent estrus was observed in one of the six F344 rats exposed to 50 mg/kg/day, one of six Donryu rats exposed to 5 mg/kg/day, and one of six Donryu rats exposed to 50 mg/kg/day. At a similar exposure duration (21 days), alterations in the estrus cycle were observed in Long-Evans and Sprague-Dawley rats administered 150 or 300 mg/kg/day atrazine via gavage (Cooper et al. 1996b). The alterations consisted of a significant increase in the percentage of days in vaginal diestrus and a significant decrease in the percentage of days in vaginal estrus (not seen in Sprague-Dawley rats dosed with 150 mg/kg/day). A study by Eldridge et al. (1994a) also investigated possible strain differences among rats exposed to atrazine for <30 days. Altered estrus cyclicity was observed at 100 mg/kg/day (lowest dose tested) in Sprague-Dawley rats and 300 mg/kg/day in F344 rats administered atrazine by gavage for 14–21 days. A long-term exposure study by Wetzel et al. (1994) identified a no effect level of 45 mg/kg/day in F344 rats following intermediate- or chronic-duration exposure. A no-effect level for estrus cycle alterations was not identified for Sprague-Dawley rats. Studies with Sprague-Dawley rats showed that as the rats aged, the effect of atrazine on the estrus cycle changed (Eldridge et al. 1999a). During the first couple of weeks of exposure to 33 mg/kg/day atrazine in the diet, an increase in diestrus was observed with no effect on the number of days in estrus. After 13–14 weeks of exposure, there was a shift in the atrazine-affected estrus cycle; the number of days in diestrus decreased and the number of days in estrus increased. This is supported by the findings of the Wetzel et al. (1994) study that significant increases in the percentage of time in estrus was seen in Sprague-Dawley rats exposed to 7 mg/kg/day atrazine in the diet for 1, 9, and 18 months, but not after 24 months of exposure.

The alterations in estrus cycle length most likely resulted from alterations in reproductive hormones. However, consistent alterations in reproductive hormone levels have not been observed across studies. In general, increases in plasma estradiol levels were associated with increases in percentage of days in estrus and increases in plasma progesterone levels were associated with increases in percentage of days in

diestrus. A significant increase in plasma estradiol levels was observed in Sprague-Dawley rats exposed to 150 mg/kg/day atrazine via gavage for 14–23 days (Eldridge et al. 1994a). However, a decrease in plasma estradiol and an increase in plasma progesterone levels were observed at 300 mg/kg/day. The study authors suggested that this may reflect a diminished ability of rats in the 300 mg/kg/day group to develop mature ovarian follicles. An increase in estradiol levels was also observed in Sprague-Dawley rats exposed to 7 mg/kg/day atrazine for 3 months, but not after 1, 9, 12, 15, 18, or 24 months (Wetzel et al. 1994). In the similarly exposed F344 rats, no alterations in estradiol levels were found, and progesterone levels were not significantly altered in either strain. In the Cooper et al. (1996b) study, significant increases in plasma progesterone levels were observed in Long Evans and Sprague-Dawley rats administered 150 mg/kg/day for 21 days. Other associated effects that have been observed include decreased ovarian and/or uterine weight in rats (Eldridge et al. 1994a), and absence of corpora lutea and well-developed ovarian follicles in Long Evans rats that went into diestrus immediately after exposure initiation (Cooper et al. 1996b). Atrazine did not affect ovulation or number of ova in rats that did cycle (Cooper et al. 1996b, 2000).

Several studies have been conducted by a single group of investigators who examined the effects of atrazine ingestion in pigs (Ćurić et al. 1999; Gojmerac et al. 1996, 1999). Pigs with observed normal estrus cycles were given 0 or 2 mg/kg body weight/day atrazine in the feed for 19 days of the estrus cycle (Gojmerac et al. 1996). The last day of treatment corresponded to day (-3) of the beginning of the next expected estrus cycle. Blood samples drawn thrice daily (at 3-hour intervals beginning at approximately 9:00 a.m.) during the first 5 days after treatment cessation showed that serum estradiol and progesterone levels were significantly altered. Estradiol levels at day (-2) of estrus were normally high and increased slightly to day (-1), then declined precipitously to day 0 and remained low during estrus. Progesterone levels during this time were normally very low from day (-2) to day 0, then gradually increased through day 2. In atrazine-treated pigs, estradiol levels were approximately 45% of normal at estrus day (-2) and remained at that level through expected estrus day 2. Progesterone levels were severely elevated (approximately 16 times normal) at estrus day (-2) and increased 3-fold to estrus day 2. These changes in hormone levels were accompanied by a short-term delay in estrus onset. Histological examination of the ovaries showed multiple ovarian follicular cysts in various stages of development or regression, persisting corpus luteum, and cystic degeneration of secondary follicles in all treated pigs. Ćurić et al. (1999) exposed pigs to atrazine in a similar manner to the above study and examined the thoracic and abdominal contents grossly and microscopically 9 days after treatment cessation. Again, multiple ovarian follicular cysts in various stages of development or regression, persisting corpus luteum, and cystic degeneration of

secondary follicles were seen, as well as a small number of atretic follicles and normal primary and secondary follicles. The uterus was in diestrus (uterine rest) instead of in estrus.

In a similar study, groups of nine female Swedish Landrace/Large Yorkshire cross pigs (6–7-month-old gilts) were administered 0 or 1 mg/kg/day atrazine in the feed for 19 days beginning with the onset of estrus (day 0) (Gojmerac et al. 1999). Blood samples were drawn 3 times daily at 3-hour intervals on the 5 days immediately following the final day of atrazine administration (this corresponded to the expected day of the next estrus [day 0] and 2 days before [days -1 and -2] and 2 days [days 1 and 2] after the expected estrus). Serum 17β-estradiol (E_2) concentrations in the blood samples were determined, and histopathological examination of the uterus was performed. E_2 concentrations were statistically significantly different ($p<0.001$) from controls on all 5 days measured. In controls, E_2 concentrations were high on days -2 and -1, then dropped on day 0 (beginning of estrus) and remained low on days 1 and 2. In treated animals, E_2 concentrations were lower than controls on days -2 and -1, and higher than controls on days 0 through 2. Treated pigs failed to exhibit overt signs of estrus onset and uterine histopathology indicated a state of uterine rest (diestrus) at the end of the observation period. A slight, but steady increase of E_2 hormone level was seen in the treated animals on day 24 of the estrus cycle (day 2). The study authors suggested that the balance of the E_2 hormone level was being gradually restored, which is the pattern that would be anticipated if the animals were about to go into estrus. Similar results were seen after administration of 0 or 2 mg/kg/day atrazine (Gojmerac et al. 1996). An intermediate-duration oral MRL of 0.003 mg/kg/day was calculated based on the LOAEL of 1 mg/kg/day in the Gojmerac et al. (1999) study.

Two studies examined the effect of atrazine on fertility. A decrease in the number of sperm positive females was seen when atrazine-exposed male and female F344 rats were mated (Šimić et al. 1994). No effect was seen when exposed males were mated with unexposed females and only a slight effect (82% sperm positive versus 100% in controls) was seen when exposed females were mated with unexposed males. No significant alterations in fertility were observed in a 2-generation rat study in which male and female Charles River albino rats were fed 27 mg/kg/day atrazine for at least 10 weeks prior to mating (EPA 1987e).

The highest NOAEL and all reliable LOAEL values for reproductive effects are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.6 Developmental Effects

A study was conducted to assess the relationship between herbicides in the drinking water supply and intrauterine growth retardation (IUGR) (Munger et al. 1997). A survey of 856 municipal drinking water supplies in Iowa found that, in 1986–1987, the Rathbun water system contained persistently elevated levels of triazine herbicides, including atrazine; the mean level of atrazine was 2.2 µg/L compared to 0.6 µg/L in other Iowa surface water supplies. Alachlor, cyanazine, metolachlor, and 2,4-D were more frequently detected in the Rathburn water supply. A comparison of rates of low birth weight, prematurity, and IUGR in live singleton births by women in 13 communities served by the affected water system to rates in other communities of similar size in the same Iowa counties during the period of 1984–1990 showed that there was a greater risk of IUGR (relative risk=1.8; 95% CI=1.2–2.6) for the Rathbun-served communities. Multiple linear regression analyses showed that levels of atrazine (regression coefficient of 1.8, R^2=0.19) as well as metolachlor (regression coefficient of 8.2, R^2=0.16), cyanizine (regression coefficient of 2.05, R^2=0.15), and chloroform (regression coefficient of 0.17, R^2=0.12) were significant predictors of community IUGR rates in the exposed populations. Several potential confounders were controlled for in the regression analysis, including maternal smoking, mothers who received poor prenatal care, and socioeconomic variables (e.g., median income, women in the workforce, and women with a high school or greater education); however, the confounding factors were measured on an ecological, rather than an individual, level. Atrazine had the best fit (R^2) in the regression model, but effects of other herbicides, which are intercorrelated, could not be ruled out. The study authors determined that there was no strong causal relationship between any single water contaminant and the risk of IUGR due, in part, to the limited ability to control for confounding factors related to source of drinking water and risk of IUGR.

The rate of birth defects was also evaluated in the Rathbun-served Iowa communities compared to other Iowa communities of similar size (Munger et al. 1992b). Birth defects were identified from the Iowa Birth Defects Registry for babies born in 1983–1989. There were excesses of cardiac defects (relative risk [RR]=3.38, 95% CI=2.07–5.48), limb reduction defects (RR=3.24, 95% CI=1.35–7.35), urogenital defects (RR=2.96, 95% CI=1.67–5.19), and all birth defects combined (RR=2.51, 95% CI=1.85–3.41) in the Rathbun communities. No significant excess of other birth defects was reported for the Rathbun communities, including cleft palate, hypertrophic pyloric stenosis, congenital dislocation of the hip, or foot deformities.

Developmental effects have been observed following pregestational, gestational, and lactational exposure of rat dams to atrazine. The observed effects included postimplantation losses, decreases in fetal body weight, incomplete ossification, neurodevelopmental effects, and impaired development of the reproductive system. In the offspring of Sprague-Dawley rats administered 70 mg/kg/day atrazine by gavage on gestational days 6–15, incomplete ossification of the skull, hyoid bone, teeth, forepaw metacarpals, and hindpaw distal phalanges were observed (Infurna et al. 1988). In a parallel study, pregnant rabbits administered 75 mg/kg/day atrazine on gestational days 7–19 had increased resorptions/litter and postimplantation losses/litter and decreased live fetuses/litter (Infurna et al. 1988). Decreased fetal body weights and nonossification of forepaw metacarpals and middle phalanges, hindpaw talus and middle phalanges, and patella were observed in the rabbit offspring. Severe maternal toxicity was also observed in the rabbits exposed to 75 mg/kg/day. No developmental effects were observed at 5 mg/kg/day. Holtzman rats exposed to 100 mg/kg/day, but not 50 mg/kg/day, atrazine on gestational days 1–8 also had increased postimplantation losses, as well as decreased serum luteinizing hormone and progesterone (Cummings et al. 2000b). Postimplantation losses were not seen at the same dose levels in Sprague-Dawley, Long-Evans, or F344 rats, although serum luteinizing hormone was decreased at 100–200 mg/kg/day (Cummings et al. 2000b). Some differences were noted between groups of rats exposed to atrazine during the afternoon (prior to the diurnal prolactin surge) and those exposed in the early morning (prior to the nocturnal prolactin surge). Narotsky et al. (2001) evaluated atrazine-induced full-litter resorption susceptibility in rats for different periods of gestation (during and after the luteinizing hormone-dependent period). Sprague-Dawley, F344, and Long Evans rats were administered 0, 25, 50, 100, 200, or 300 mg/kg/day atrazine by gavage on gestation days 6 through 10. The rats were allowed to deliver, and the number of implantation sites was recorded. F344 rats administered atrazine exhibited dose-related incidences of full-litter resorption (63, 80, and 100% at 100, 200, and 300 mg/kg/day, respectively). F344 rats exposed to 200 mg/kg atrazine that maintained their litters had increased prenatal loss, decreased litter size, and reduced pup weights (Narotsky et al. 2001).

No developmental effects were noted in a 2-generation study in which Charles River albino rats were exposed to 31 mg/kg/day atrazine in the diet (EPA 1987e). No alterations in the number of pups per litter or weaning weight of pups were observed in the offspring of four rats (strain not specified) exposed to up to 113 mg/kg/day atrazine in the diet on gestational days 1–21 (Peters and Cook 1973).

Studies by Peruzović et al. (1995) and Stoker et al. (1999, 2000) examined the effect of pregestational or lactational exposure to atrazine on the development of the nervous and reproductive systems. In the Peruzović et al. (1995) study, female Fischer rats were administered via gavage 0 or 120 mg/kg purified

atrazine every 48 hours for 12 days. Four weeks after the cessation of treatment, rats were mated with untreated males and allowed to carry to term and deliver pups. Litter size, pup weight, and pup survival were not statistically different between control and treated groups. At 70 days of age, the offspring were tested for spontaneous activity by recording ambulatory activity in 4 time blocks of 15-minutes each. Avoidance response was tested at 72 days of age and extinction response was tested at 73 days of age. Mild neurobehavioral effects were observed and differences were noted between male and female offspring. Female offspring of atrazine-treated dams had a statistically significant ($p<0.05$) higher spontaneous activity level than the female offspring of control dams during the first 15 minute block; no differences were seen between groups of male offspring. In the avoidance conditioning trials, male offspring of treated dams had statistically significant ($p<0.05$) shorter latency times and increased number of avoidances, compared to control offspring. Conversely, female offspring of atrazine-treated dams had longer latency times and decreased number of avoidances, compared to controls, but without statistical significance. No statistical differences between treated and control groups were seen in the extinction tests (Peruzović et al. 1995).

Adult male offspring of Wistar rat dams administered up to 50 mg/kg/day atrazine on lactational days 1–4 had increased incidence and severity of inflammation of the lateral prostate, increased myeloperoxidase levels in the prostate, and increased total DNA in the prostate (Stoker et al. 1999). These effects are hypothesized to be indirect effects mediated by a lack of prolactin release in the dam in response to pup suckling; this hypothesis was supported in this study by the elimination of increased prostate inflammation in the offspring in response to co-administration of prolactin with atrazine to the dams. The level of myeloperoxidase, a lysosomal enzyme found primarily in neutrophils and macrophages, was used as an indication of the severity of inflammation. Histological examination also found increases in the incidence of focal luminal polymorphonuclear inflammation and focal interstitial mononuclear inflammation in lateral prostates at 120 days of age in the 25 and 50 mg/kg groups. Offspring of rat dams receiving atrazine on lactational days 6–9 had only statistically insignificant increases in prostate inflammation, and offspring of dams receiving atrazine on lactational days 11–14 had no increase in prostate inflammation (Stoker et al. 1999).

Male rats exposed to 50 mg/kg/day atrazine or higher on postnatal days 23–53 had decreased ventral prostate weights and delayed preputial separation, which is a marker of male puberty in the rat (Stoker et al. 2000). Dose-related increases in serum estrone and estradiol concentrations and serum triiodothyronine were only significant in rats exposed to 200 mg/kg/day. No histopathological changes

were seen in the thyroid and only mild hypospermia was seen in some high-dose rats, which may be a result of delayed puberty.

Studies by Laws et al. (2000) and Ashby et al. (2002) investigated the effect of peripubertal exposure to atrazine on the reproductive development of female rats. Female Wistar rats exposed to 50, but not 25, mg/kg/day atrazine from 20 to 41 days of age had delayed vaginal opening, which is a marker of female puberty in the rat (Laws et al. 2000). The age of the first 4–5-day estrus cycle after vaginal opening was also delayed; estrus cycles were normal within 3–4 weeks after cessation of atrazine exposure (Laws et al. 2000).

Ashby et al. (2002) administered atrazine to female Wistar and Sprague-Dawley rats at doses of 10, 20, 30, and 100 mg/kg/day on postnatal days 21–46. Delayed uterine growth was observed in female Wistar rats exposed to 100 mg/kg/day of atrazine at postnatal days 30 and 33, but was normal by postnatal day 43. Uterine weights in Sprague-Dawley rats were unaffected by day 46 (Ashby et al. 2002). Vaginal opening was significantly delayed in Sprague-Dawley rats exposed to atrazine at 30 and 100 mg/kg/day and in Wistar rats at 100 mg/kg/day by postnatal day 46 (Ashby et al. 2002).

3.2.2.7 Cancer

An ecological study in Ontario, Canada, that examined the association of atrazine in the drinking water supply with cancer incidence rates found a positive association between atrazine levels and stomach cancer ($p=0.046$ and $p=0.242$ for males and females, respectively) (Van Leeuwen et al. 1999). For men, this corresponded to an observed increase of 0.6 cases of stomach cancer per 100,000 person-years at risk for each 100 ng/L increase in atrazine levels in drinking water. For women, for each 50 ng/L increase in atrazine levels in drinking water, there was an observed increase of 1.0 stomach cancer cases per 100,000 person-years at risk. Statistically significant ($p\leq0.04$) negative associations were noted between atrazine levels and colon cancer in males and females; it was not ascertained what may have caused this result. There were no statistically significant associations between atrazine exposure and ovarian cancer or non-Hodgkin's lymphoma in females. In males, there was a negative association between atrazine exposure and non-Hodgkin's lymphoma, but the association was not statistically significant ($p=0.075$). Data were collected and analyzed for ecodistricts; no individual data were used or provided. The average atrazine contamination level was 162.74 ng/L (range of 50–649 ng/L) and potential confounding

variables, including alcohol consumption, smoking, education level, income, and occupational exposures, were considered.

An association between exposure to triazines and breast cancer incidence rates in women was found in an ecological study conducted in 120 Kentucky counties (Kettles et al. 1997). Two-year age-adjusted breast cancer rates for 1991–1992 and 1993–1994 were calculated from state registry data. Although atrazine levels were unavailable, it is likely that much of the triazine exposure was due to atrazine since it is the most widely used herbicide in Kentucky. Triazine exposure data were generated using estimated exposures based on water contamination (the mean triazine level in groundwater was 0.11±0.19 µg/L), county corn crop production (in acres), and county pesticide use. Based on these data, the Kentucky counties were classified as having low, medium, or high exposure levels. Confounding variables, including age, race, income, and education level, were controlled for. Breast cancer risk based on 1993–1994 breast cancer rates was significantly increased in women in counties having medium (OR=1.14; 95% CI=1.08–1.19) and high (OR=1.2; 95% CI=1.13–1.28) triazine exposure levels.

Another ecological study was conducted in Kentucky (120 counties) to examine the association between atrazine in the drinking water and incidence of breast and ovarian cancers (Hopenhayn-Rich et al. 2002) in 1993–1997. Data were obtained from state records on ovarian and breast cancer age-adjusted incidence rates, amount of atrazine in drinking water (mean concentration in all 120 counties ranged from 0.21 to 1.39 µg/L), pounds of atrazine sold, and acres of corn planted. No significant association was found between atrazine exposure and the incidence of breast or ovarian cancer in Kentucky women. The race- and education-adjusted rate ratios for women with the highest atrazine exposure were 0.96 (95% CI=0.92–1.01) and 0.85 (95% CI=0.73–0.98), respectively. Similar results were found when acres of corn planted and atrazine sales by geographic location were used as surrogates for atrazine exposure.

A number of animal studies have examined the carcinogenic potential of atrazine in animals. In F344/LATI rats administered atrazine via the diet, significant increases in the number of rats with malignant tumors and total benign mammary gland tumors were observed in male rats exposed to 65 mg/kg/day (Pintér et al. 1990). However, no significant increase was seen in any specific tumor type. It is likely that the mammary tumors were an effect of increased survival of treated rats rather than dietary atrazine administration. Thakur et al. (1998) noted that six of eight high-dose mammary tumors appeared after the last control died at week 111 and that the increase in mammary tumors in treated male rats was not significant when adjusted for survival. Female rats receiving a dietary level of 65 mg/kg/day had statistically significant increased incidences of leukemia/lymphoma (22/51 versus 12/44 in controls) and

uterine adenocarcinoma (13/45 versus 6/45 in controls). The overall proportion of benign and malignant uterine tumors in treated females was similar to controls (16/45, 19/52, and 17/45 for 0, 32, and 65 mg/kg/day, respectively). In addition, it was pointed out that the female leukemia/lymphoma data should not have been combined because these two cancer types are of different origins in Fischer rats; when the tumor types were separated, there was no longer a significant trend in treated rats (Thakur et al. 1998). Another study of Fischer rats found no significant increases in the incidences of mammary or pituitary tumors after two years of dietary exposure to doses as high as 45 mg/kg/day (Wetzel et al. 1994).

In contrast, several studies have found increases in tumor incidences in female Sprague-Dawley rats. Three of these studies were submitted to EPA as confidential business information and are not publicly available; reviews of these studies were published by Stevens et al. (1994, 1999). As reported by Stevens et al. (1994, 1999), two of these studies found significant increases in the incidence of mammary fibroadenomas in female Sprague-Dawley rats exposed to 71–80 mg/kg/day via the diet for 106 weeks or a lifetime; no significant alterations were found at 35 mg/kg/day and lower. The third study, a two-generation study, did not find significant alterations in the incidence of mammary tumors in F2 females after 2 years of exposure to ≤40 mg/kg/day in the diet. Additionally, one study found an increase in mammary adenocarcinomas following 106 weeks of dietary exposure to ≥5 mg/kg/day. An increase in interstitial cell tumors were observed in the testes of Sprague-Dawley rats following lifetime exposure to 52 mg/kg/day in the diet; this was attributed to increased survival in this group. Wetzel et al. (1994) found similar results in female Sprague-Dawley rats. In this study, statistically significant increases in earlier onset of mammary and pituitary tumors were observed in animals killed or dying during the first 54 weeks of exposure to 39 mg/kg/day; these effects were not noted in rats exposed to 7 mg/kg/day (Stevens et al. 1999; Wetzel et al. 1994). No significant alterations in the incidence of mammary or pituitary tumors were found between weeks 55 and 105. There were no significant increases in malignancies in any treatment group for the entire study period (0–105 weeks), likely due to age-related increases in tumors in the controls. Mammary and pituitary tumors appeared earlier in rats treated with atrazine, apparently due to the mechanism of reproductive senescence in Sprague-Dawley rats (see Sections 3.5.2 and 3.5.3).

Another unpublished study discussed by Stevens et al. (1999) compared the carcinogenicity of atrazine in ovariectomized and intact female Sprague-Dawley rats exposed to atrazine in the diet for 2 years. Significantly increased mortality was noted in intact rats at 32 mg/kg/day, but mortality was not significantly affected in ovariectomized rats at the same exposure level. Intact rats had increased

incidences of mammary carcinomas at 4 and 32 mg/kg/day (but not at 2 or 6 mg/kg/day) and mammary fibroadenomas at ≥4 mg/kg/day. No mammary tumors were found in any treated ovariectomized rats.

Two unpublished studies of male and female CD-1 mice reviewed by Stevens et al. (1999), did not find significant increases in the incidence of neoplastic changes in males exposed to 386 mg/kg/day or females exposed to 483 mg/kg/day in the diet for ≥91 weeks. Similarly, no significant alterations in tumor incidences were observed in mice administered by 22 mg/kg/day atrazine by gavage in a 0.5% gelatin vehicle from 7 days old until 4 weeks old and then in the diet with no vehicle for 18 months (Innes et al. 1969).

The available oral carcinogenicity data in animals suggest that high doses atrazine in the diet result in an increased incidence and earlier onset of mammary tumors in female Sprague-Dawley rats as compared to age-matched controls; however, these effects are not found in similarly exposed female Fischer 344 rats or CD-1 mice.

CEL values from each reliable study in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies regarding death in humans following dermal exposure to atrazine were located.

The acute (14-day) dermal LD_{50} in rats has been reported to be >2,500 mg/kg/day (Gaines and Linder 1986).

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, ocular, and body weight effects in humans and/or animals after dermal exposure to atrazine.

Dermal Effects. A 40-year-old white male farmer developed blisters on his hands and forearms one afternoon after having applied atrazine to crops in the morning using a spray rig and cleaning the plugged nozzles several times with his hands (Schlicher and Beat 1972). By 14 hours later, both hands and forearms had painful erythematous eruptions with blistering and swelling. The diagnosis was acute contact dermatitis, and treatment resulted in complete recovery. The farmer had also applied a second herbicide (Bladex=2-[4-chloro-6-ethylamino-s-triazin-2-ylamino]-2-methylpropionitrile) in the same afternoon; therefore, the exact cause of the dermatitis was not discernable.

3.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans and/or animals after dermal exposure to atrazine.

3.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans and/or animals after dermal exposure to atrazine.

3.2.3.5 Reproductive Effects

Results of a survey of farm couples in Ontario, Canada, to assess reproductive effects of pesticides indicated weak to moderate associations between atrazine use on crops and in the yard with an increase in preterm delivery and with miscarriage (Arbuckle et al. 2001; Savitz et al. 1997). Other results from this survey of Ontario farm couples indicated that atrazine was not associated with any decrease in fecundity as a result of effects on spermatogenesis (Curtis et al. 1999). In these cohort studies, it is probable that the application of atrazine involved both inhalation and dermal exposure; most of the women were indirectly exposed, possibly through contact with contaminated clothes or contaminated drinking water (for additional study details, see Section 3.2.1.5 Inhalation Reproductive Effects).

No studies were located regarding reproductive effects in animals after dermal exposure to atrazine.

3.2.3.6 Developmental Effects

The results of a survey of 1,898 farm couples living year-round on farms in Ontario, Canada, designed to assess reproductive effects of pesticides, indicated that the sex ratio was not altered and the risk of small for gestational age deliveries was not increased in relation to pesticide exposure (atrazine exposure level not available) (Savitz et al. 1997). It is probable that the pesticide application resulted in both dermal and inhalation exposure.

No studies were located regarding developmental effects in animals after dermal exposure to atrazine.

3.2.3.7 Cancer

Several studies were located regarding cancer incidence and exposure of humans to atrazine. Although the exposure route was not specified in these studies, it is probable that dermal (e.g., handling and use of atrazine), inhalation (e.g., application of atrazine), and perhaps even oral (e.g., due to groundwater contamination) exposure occurred. These population-based case-control studies found some suggestive evidence of positive associations between atrazine use and brain, testes, and prostate cancers (Mills 1998), leukemia (Mills 1998), and non-Hodgkin's lymphoma (Mills 1998; Weisenburger 1990; Zahm et al. 1993b). Limitations of these studies included small sample sizes, lack of specific exposure data, and exposure to chemicals other than atrazine. Further details on these studies can be found in Section 3.2.1.7.

No studies were located regarding cancer in animals after dermal exposure to atrazine.

3.2.4 Other Routes of Exposure

Hematological Effects. Mice injected intraperitoneally with a single dose of 58.65 mg/kg atrazine showed changes in some hematological parameters (Mencoboni et al. 1992). Transient, but precipitous, decreases were seen in peripheral blood reticulocytes, bone marrow morphologically recognizable precursors, granulocyte-macrophage committed progenitors, and pluripotent stem cells. Peripheral blood leukocytes were not altered.

Hepatic Effects. Fischer rats injected intraperitoneally with atrazine showed dose- and time-dependent changes in liver enzymes (Islam et al. 2002). Induction of P-glycoprotien (a pre-neoplastic and neoplastic marker in the liver) began at doses of 50 mg/kg atrazine and reached maximum induction at 300 mg/kg atrazine. P-Glycoprotein induction was also determined to be time-dependent as induction increased from day 1 to day 5 of exposure to 300 mg/kg atrazine. Glutathione-S-transferase (also a neoplastic marker) was induced at the low dose of 10 mg/kg atrazine (Islam et al. 2002).

Neurological Effects. Sprague-Dawley rats injected intraperitoneally with 0, 85, or 170 mg/kg atrazine twice a week for 30 days showed some transient neurological effects (Castano et al. 1982). No alterations were seen electron microscopically in the cervical or thoracic ganglia, spinal cord, or sciatic nerve of rats killed immediately after the end of the treatment period. However, morpho-quantitative analysis revealed decreased areas for myelinated and unmyelinated axons in the 170 mg/kg group; statistical significance was reached only for unmyelinated axons. Recovery was seen after 30 days of nontreatment. Morpho-quantitative analysis involved computer analysis of electron micrographs of the sciatic nerve for cross-sectional area of myelinated and unmyelinated fibers and for thickness of myelin sheaths.

Reproductive Effects. Intraperitoneal exposure to atrazine has been shown to effect sperm parameters including testicular sperm count, epididymal sperm numbers, and sperm mobility. In adult male Fischer rats administered 0, 60, or 120 mg/kg/day atrazine intraperitoneally twice a week for a period of 60 days, relative weights of the pituitary and ventral prostate were significantly decreased in both treatment groups (Kniewald et al. 2000). Testicular sperm numbers were increased in both treatment groups, and a dose-related decrease in epididymal sperm number was seen; testicular sperm numbers in controls decreased during the study, indicating normal sperm migration to the epididymis. Epididymal sperm motility was also decreased in both treatment groups by about 50% (motility in controls was about 50% and in treated groups was 21–25%). The activity of alpha-glucosidase in the epididymis was decreased in both treatment groups. Histological examination revealed decreased spermatogenesis and cell disorganization. Electron microscopy showed interstitial cells with acidophilic, differently vacuolated cytoplasm and smooth nuclei with visible nucleoli, lower cell density, and a decrease in the unit number of cells; collagen fibers were reduced and dispersed in the interstitial space; Leydig cells were small and misshapen with cytoplasms filled with lysosomes and vacuoles and the nucleus was invaginated; the morphology of the rough and smooth endoplasmic reticulum in Leydig cells was altered; and degenerative changes were seen in Sertoli cells. Male Fischer rats intraperitoneally exposed to atrazine 2 times/week for 60 days at doses of 3, 7.5, 15, 30, 60, and 120 mg/kg/day showed a significant

decrease in testicular sperm counts when exposed to 3 mg/kg/day. There was also a significant decrease in epididymal sperm number and sperm mobility at doses of 3 and 15 mg/kg/day, respectively (Simic et al. 2001). Increases of pituitary and prostrate weights were observed.

Developmental Effects. Peters and Cook (1973) conducted a set of studies examining the subcutaneous administration of high doses of atrazine to pregnant rats to determine the effects on live pups/litter and resorption sites. In rat dams exposed on gestational days 3, 6, and 9, postimplantation losses were increased at 800 mg/kg/treatment day, but not at 200 mg/kg/treatment day. In dams exposed for only 1 day (gestational day 3, 6, or 9), no dose-related increases in postimplantation losses were observed (Peters and Cook 1973). Although pups/litter were decreased in the 1,000 mg/kg group exposed on gestational day 6, there was no effect in the 2,000 mg/kg group exposed similarly.

Cancer. Thirty male Swiss albino mice were administered atrazine intraperitoneally once every 3 days for 13 injections for a total dose of 0.26 mg/kg body weight (Donna et al. 1986). Two additional groups of 30 mice (one group followed the same treatment schedule with intraperitoneal injections of saline and one group received no treatment) served as controls. A statistically significant ($p<0.001$) increase in lymphomas (affecting mesenteric, lumbar, periaortic, and mediastinal lymph nodes) was reported in the atrazine-treated mice; six animals died of lymphomas during the study period.

3.3 GENOTOXICITY

Numerous *in vivo* and *in vitro* studies have assessed the genotoxic potential of atrazine, and the results of these studies are presented in Tables 3-2 and 3-3, respectively.

Several studies have examined the *in vivo* genotoxicity of atrazine in rats, mice, and *Drosophila*; no *in vivo* human genotoxicity studies were located. A weak positive result for dominant lethal effects in mouse spermatids was seen following a single oral dose of 1,500 mg/kg (Adler 1980). No significant increase in mutagen levels were seen in the urine of rats treated with 50 mg/kg atrazine for 5 weeks using a modified Ames assay (George et al. 1995). An increased occurrence of DNA strand breaks were observed in the stomach, liver, and kidneys, but not in the lungs, of rats that received a single dose of 875 mg/kg or 15 daily doses of 350 mg/kg atrazine (Pino et al. 1988). A significant increase of DNA damage in leukocytes, as measured by tail moment, was observed in mice that received a single dose of 250 or 500 mg/kg atrazine (Tennant et al. 2001). An increased occurrence of micronucleus formation was

Table 3-2. Genotoxicity of Atrazine *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Rat stomach, liver, kidney	DNA strand breaks	+	Pino et al. 1988
Rat lung	DNA strand breaks	–	Pino et al. 1988
Mouse bone marrow, female	Micronucleus formation	+	Gebel et al. 1997
Mouse bone marrow, male	Micronucleus formation	–	Gebel et al. 1997
Mouse bone marrow	Chromosomal aberrations	–	Meisner et al. 1992
Mouse bone marrow, female	Micronucleus formation	–	Kligerman et al. 2000b
Mouse leukocytes, female	DNA damage	+	Tennant et al. 2001
Nonmammalian cells:			
Drosophila melanogaster	Somatic mutation	+	Torres et al. 1992
D. melanogaster	Somatic mutation	+	Tripathy et al. 1993
D. melanogaster	Dominant lethal mutation	+	Murnik and Nash 1977
D. melanogaster	Aneuploidy	+	Murnik and Nash 1977

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

Table 3-3. Genotoxicity of Atrazine *In Vitro*

Species (test system)	End point	With activation	Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium	Forward mutation	–	–	Adler 1980
S. typhimurium	Reverse mutation	–	–	Kappas 1988
S. typhimurium	Reverse mutation	+	No data	Means et al. 1988
S. typhimurium	Reverse mutation	–	No data	Bartsch et al. 1980; Sumner et al. 1984
S. typhimurium	Reverse mutation	–	–	Adler 1980; Lusby et al. 1979; Morichetti et al. 1992; Ruiz and Marzin 1997; Zeiger et al. 1988
S. typhimurium	Reverse mutation	No data	–	Andersen et al. 1972; Butler and Hoagland 1989; Seiler 1973
Esherichia coli PQ37	SOS repair	–	–	Ruiz and Marzin 1997
E. coli	Forward mutation	–	–	Adler 1980
Bacteriophage T4	Forward mutation	No data	–	Andersen et al. 1972
Bacteriophage	Reverse mutation	No data	–	Andersen et al. 1972
Eukaryotic organisms:				
Saccharomyces cerevisiae	Mitotic recombination	No data	–	Emnova et al. 1987
S. cerevisiae	Gene conversion	+	–	Plewa and Gentile 1976
S. cerevisiae	Gene conversion	–	–	Adler 1980
S. cerevisiae	Gene conversion, stationary phase	+	–	Morichetti et al. 1992
S. cerevisiae	Gene conversion, logarithmic phase	+	–	Morichetti et al. 1992
S. cerevisiae	Reverse mutation, stationary phase	No data	–	Morichetti et al. 1992
S. cerevisiae	Reverse mutation, logarithmic phase	No data	+	Morichetti et al. 1992
S. cerevisiae	Forward mutation	No data	+	Emnova et al. 1987
Aspergillus nidulans	Gene conversion	No data	–	de Bertoldi et al. 1980
A. nidulans	Mitotic recombination	+	–	Adler 1980
A. nidulans	Mitotic recombination	–	–	Kappas 1988
A. nidulans	Forward mutation	+	–	Benigni et al. 1979
A. nidulans	Aneuploidy	+	–	Benigni et al. 1979
Neurospora crassa	Aneuploidy	No data	+	Griffiths 1979
Schizosaccharomyces pombe	Reverse mutation	+	–	Mathias et al. 1989
Tradescantia paludosa	Micronucleus formation	+	–	Mohammed and Ma 1999

Table 3-3. Genotoxicity of Atrazine *In Vitro*

Species (test system)	End point	With activation	Without activation	Reference
Mammalian cells:				
Human lymphocytes	DNA damage	–	+	Ribas et al. 1995
Human lymphocytes	DNA damage	–	–	Ribas et al. 1998
Human lymphocytes	DNA damage	–	–	Ribas et al. 1998
Human lymphocytes	Sister chromatid exchange	–	–	Dunkelberg et al. 1994
Human lymphocytes	Sister chromatid exchange	No data	+	Lioi et al. 1998
Human lymphocytes	Chromosomal aberrations	No data	+	Lioi et al. 1998
Human lymphocytes	Chromosomal aberrations	No data	+	Meisner et al. 1992, 1993
Human lymphocytes	Chromosomal aberrations	No data	–	Kligerman et al. 2000a
Human lymphocytes	DNA repair	No data	–	Surralles et al. 1995
Chinese hamster cells	Chromosomal aberrations	No data	–	Ishidate 1998

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

observed in the bone marrow of female NMRI mice receiving a single dose of 1,400 mg/kg/day atrazine, but not in bone marrow cells from male mice dosed with 1,750 mg/kg (Gebel et al. 1997), or female mice dosed with up to 500 mg/kg atrazine (Kligerman et al. 2000b). No chromosome damage was seen in the bone marrow of mice administered 20 ppm atrazine in the drinking water for 90 days (Meisner et al. 1992; Roloff et al. 1992), but increased chromosome breakage was observed in cultured splenocytes from the treated mice (Roloff et al. 1992). Tests for somatic mutation (Torres et al. 1992; Tripathy et al. 1993), dominant lethal mutations (Murnick and Nash 1977) and aneuploidy (Murnick and Nash 1977) in *Drosophila melanogaster* have been positive. Atrazine was not clastogenic in the newt micronucleus test (L'Haridon et al. 1993), but DNA damage was seen in *Rana catesbeiana* tadpoles exposed to 4 µg/mL atrazine (Clements et al. 1997).

A number of *in vitro* studies have examined the genotoxicity of atrazine in bacterial, yeast, and human lymphocyte assays. In general, atrazine did not increase the formation of forward mutations (Adler 1980) or reverse mutations (Adler 1980; Andersen et al. 1972; Bartsch et al. 1980; Butler and Hoagland 1989; Kappas 1988; Lusby et al. 1979; Morichetti et al. 1992; Ruiz and Marzin 1997; Seiler 1973; Sumner et al. 1984; Zeiger et al. 1988) in *Salmonella typhimurium* with or without metabolic activation; Means et al. (1988) reported an increase in reverse mutations with metabolic activation. Studies in *Escherichia coli* have been negative for SOS repair (Ruiz and Marzin 1997) and forward mutations (Adler 1980); the occurrences of forward or reverse mutations were also not increased in bacteriophages (Andersen et al. 1972). In contrast to the results found in prokaryotic organisms, most assays in eukaryotic organisms showed evidence of genotoxicity. Increases in the occurrence of gene conversion (Morichetti et al. 1992; Plewa and Gentile 1976), reverse mutations (Morichetti et al. 1992), and forward mutations (Emnova et al. 1987) were observed in *Saccharomyces cerevisiae*. In *Aspergillus nidulans*, increases in the occurrence of mitotic recombination (Adler 1980), forward mutation (Benigni et al. 1979), and aneuploidy (Benigni et al. 1979) were observed; however, Kappas (1988) did not observe the occurrence of mitotic recombination in *A. nidulans*. Gene conversion was also not observed in *A. nidulans* (de Bertoldi et al. 1980). An increase in the occurrence of aneuploidy was seen in *Neurospora crassa* Griffiths 1979). Reverse mutations in *Schizosaccharomyces pombe* (Mathias et al. 1989) and micronucleus formation in *Tradescantia paludosa* (Mohammed and Ma 1999) have also been reported.

In mammalian cells, several studies showed no increase in the occurrence of chromosomal aberrations observed in Chinese hamster cells (Adler 1980; Ishidate 1988), while others did observe DNA damage (Biradar and Rayburn 1995a, 1995b; Taets et al. 1998). There have also been conflicting results in studies concerning the genotoxicity of atrazine to human lymphocytes. In human lymphocytes, an

increase in DNA damage was observed (Ribas et al. 1995); a later study by this group (Ribas et al. 1998) did not confirm this finding. Meisner et al. (1992, 1993) and Lioi et al. (1998) observed increased chromosomal aberrations in human lymphocytes, while Kligerman et al. (2000a) and Ghiazza et al. (1984) did not observe any significant increases in the occurrence of chromosomal aberrations. The occurrences of sister chromatid exchange in human lymphocyte cells were not found to be altered in several studies (Dunkelberg et al. 1994; Kligerman et al. 2000a; Ribas et al. 1998); in contrast, Lioi et al. (1998) did observe increased sister chromatid exchange. An excision repair assay in human lymphocytes without activation, did not result in DNA damage (Surralles et al. 1995).

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were located that measured absorption or monitored metabolites in excreta of humans or animals exposed to atrazine only via the respiratory route. The only available inhalation toxicity studies involved exposure to very large atrazine particles (30–70 μm) (Catenacci et al. 1990, 1993), which made it unlikely that any significant amount of atrazine reached the lungs.

3.4.1.2 Oral Exposure

Absorption of atrazine in humans following oral exposure was indicated in a single case report of a 38-year-old man who died of progressive organ failure and shock 3 days after ingesting 500 mL of a weedkiller that contained 100 g atrazine, 25 g of aminotriazole, 25 g of ethylene glycol, and 0.15 g of formaldehyde (Pommery et al. 1993). At autopsy, atrazine was detected in the kidney, small intestine, lung, liver, pancreas, muscle, heart, and plasma.

In rats gavaged with a single dose of 30 mg/kg [^{14}C]-atrazine in aqueous solution, radioactivity levels in plasma peaked 8–10 hours postdosing (Timchalk et al. 1990). The absorption of radioactivity (K_a) was described as a first-order process and was used to calculate an absorption half-life of 2.6 hours. Approximately 66% of the administered radioactivity was excreted in the urine over a 72-hour monitoring period. About half of this amount appeared in the urine within the first 12 hours after dosing, and an

additional 20% was detected within the next 12 hours. Over the 72-hour monitoring period, about 18% of the administered radioactivity was detected in the feces, suggesting that total absorption amounted to 82% of the administered does (100% minus 18% in the feces). In a similar study, Meli et al. (1992) administered a singe dose of 50 mg/kg of atrazine in dimethylsulfoxide (DMSO) and recovered approximately 37% of the administered dose in the urine over a 96-hour period. Most of the dose was absorbed within the first 24 hours. The reason for the apparent discrepancy in the amounts absorbed (as determined only by urinary excretion) between the two studies is unknown, but it is possible that the different vehicles may have played a role.

3.4.1.3 Dermal Exposure

Data regarding dermal exposure to atrazine in humans indicate that limited absorption occurs. Buchholz et al. (1999) applied dermal patches containing ring-radiolabeled atrazine mixed with the commercial atrazine product Aatrex to the forearms of 10 healthy male subjects for 24 hours. Unabsorbed radio-activity and the radioactivity excreted in urine and feces were measured for the 7-day period including and following the application. Quantitative data presented for three subjects indicate that 91–94% of the applied dose was not absorbed. Only 0.3–5.1% of the applied dose was absorbed as monitored by the radioactivity recovered in the urine and feces. An *in vitro* study using human skin samples exposed to [^{14}C]-atrazine found that approximately 16.4% was absorbed in a 24-hour period, and that most of the absorbed atrazine (12% of the applied dose) remained in the skin (Ademola et al. 1993). Less than 5% progressed through the skin and into receptor fluid. Dermal absorption of atrazine in humans has also been indicated by occupational studies that found atrazine and its metabolites in the urine of workers exposed primarily via dermal contact (Catanacci et al. 1990, 1993).

A single study in rats compared the dermal absorption of [^{14}C]-atrazine in young and adult rats (Hall et al. 1988) by measuring the fractional skin penetration (radioactivity in the body, skin, and excreta divided by the total radioactivity recovered in the body, skin, excreta, and unabsorbed atrazine on the application blister). The fractional skin penetration values indicated slightly higher absorption in young rats (3.2–9.6%) than in adult rats (2.8–7.7%), and decreased percent absorption with increasing atrazine dose. It is unclear what caused the difference in absorption between young and adult rats; skin thickness was almost identical in the two groups and, therefore, was not a factor. No data are available on the transport mechanism of atrazine in skin. Dermal absorption may be limited by saturation of the transport mechanism or by physical/chemical restrictions and interactions; this hypothesis is supported by an *in*

vitro study showing a percentage decrease in metabolite formation with increasing atrazine dose to human skin samples (Ademola et al. 1993).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located regarding distribution of atrazine after inhalation exposure in humans or animals.

3.4.2.2 Oral Exposure

Data on distribution of atrazine in humans after oral exposure were limited to a single case report of a 38-year-old man who died of progressive organ failure and shock 3 days after ingesting 500 mL of a weedkiller that contained 100 g atrazine, 25 g of aminotriazole, 25 g of ethylene glycol, and 0.15 g of formaldehyde (Pommery et al. 1993). At autopsy, atrazine was detected in the kidney, small intestine, lung, liver, pancreas, muscle, heart, and plasma. The highest concentration was found in the kidney and the lowest concentration was found in the heart.

In male Fischer rats that received a single dose of 30 mg/kg [^{14}C]-atrazine by gavage, plasma levels of radioactivity peaked at 8–10 hours postdosing and the rate of clearance was apparently first-order with a half-life of 10.8–11.2 hours (Timchalk et al. 1990). Radioactivity was also determined for the whole skin and for the rest of the carcass and found to be 1.5 and 4%, respectively, of the administered dose.

In rats administered about 1.5 or 17.7 mg/kg [^{14}C]-atrazine by gavage, the majority of the radioactivity was recovered in the urine (65.5%) and feces (20.3%) over the course of 8 days (Bakke et al. 1972). The whole carcass contained 15.8% of the radioactivity 3 days after exposure, and radioactivity was detected in liver, brain, heart, lung, kidney, digestive tract, omental fat, and skeletal muscle on days 2, 4, and 8. Fate and skeletal muscle had the lowest amount of radioactivity, whereas the liver and kidney had the highest amounts. In all of the organs monitored, the levels of radioactivity decreased over time.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution of atrazine after dermal exposure in humans or animals.

3.4.3 Metabolism

Atrazine is extensively and rapidly metabolized as indicated by plasma levels of atrazine and the relative amounts of metabolites and parent compound in the urine within 8–24 hours after exposure. Plasma levels of ^{14}C from radiolabeled atrazine have been shown to peak at 8–10 hours postexposure in rats, and the elimination half-life has been calculated to be 10.8–11.2 hours (Timchalk et al. 1990). In urine, unchanged atrazine has been detected, but comprised <2% of all atrazine-related compounds after dermal exposure in humans (Buchholz et al. 1999; Catenacci et al. 1993) or oral exposure in rats (Meli et al. 1992). In humans, 50% of all urinary atrazine metabolites were excreted within 8 hours and 100% within 24 hours (Catenacci et al. 1993). In rats, approximately 57% of the radioactivity from administered [^{14}C]-atrazine was excreted in the urine within 24 hours (Timchalk et al. 1990), and urinary atrazine metabolites decreased to 1/30 or less of the 24-hour level by 48 hours postexposure (Meli et al. 1992).

Atrazine is primarily metabolized in humans via dealkylation, probably followed by glutathione conjugation and conversion to mercapturic acids. In humans exposed to [^{14}C]-atrazine dermally (via a patch on the forearm) for 24 hours, atrazine mercapturate was positively identified and a variety of other metabolites (deethylatrazine, didealkylatrazine and didealkylatrazine mercapturate, deethylatrazine mercapturate, and deisopropylatrazine) were tentatively identified in the urine (Buchholz et al. 1999). Metabolites found in the urine of male workers in an atrazine production plant were didealkylated atrazine (80%), deisopropylatrazine (10%), deethylatrazine (8%), and unmodified atrazine (1–2%) (Catenacci et al. 1993). Atrazine has also been shown to be metabolized to the mono- and di-dealkylated derivatives in human skin samples *in vitro* (Ademola et al. 1993). These human data are supported by *in vivo* animal data showing the same mono- and di-dealkylated and mercapturic acid atrazine metabolites in rat urine (Bakke et al. 1972; Meli et al. 1992; Timchalk et al. 1990) and tissues (Gojmerac and Kniewald 1989) and in chicken excreta (Foster and Khan 1976). The presence of mercapturic acid metabolites in human and rat urine indicates that phase II metabolism of atrazine probably proceeds via glutathione conjugation and conversion to mercapturic acids in the kidneys before excretion.

In vitro studies using microsomal preparations from liver and other tissues of humans and animals have indicated that dealkylation of atrazine is mediated by cytochrome P-450 enzymes (CYPs) (Adams et al. 1990; Ademola et al. 1993; Croce et al. 1996; Hanioka et al. 1998a, 1999; Lang et al. 1996, 1997; Meli et al. 1992; Venkatesh et al. 1992). Ademola et al. (1993) observed a lack of atrazine metabolism in human skin microsomal preparations in the absence of NADPH and a 70% reduction in the rate of metabolite formation when the CYP inhibitor, SKF 525-A, was added to the mixture. A similar requirement of NADPH for atrazine metabolism was noted in liver microsomal preparations of all species tested. Adams et al. (1990) determined that NADH, and therefore cytochrome b_5, were not necessary and did not contribute to atrazine metabolism in microsomal preparations. Lang et al. (1997) performed a series of experiments to determine the CYP(s) responsible for atrazine metabolism in human liver microsomes. Inclusion of seven inhibitors of specific CYPs in separate microsomal incubations showed that only α-naphthoflavone and furafylline, two CYP1A2 inhibitors, inhibited the production of dealkylation products. Additionally, when cDNA-expressed CYPs (1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) were used in incubations similar to microsomal preparations, CYP1A2, and to a lesser extent 2C19 and 1A1, produced deisopropyl- and deethylatrazine (Lang et al. 1997). These data implicate CYP1A2 as the primary enzyme involved in phase I metabolism of atrazine in humans. Studies in rat liver microsomes suggested that CYP2B1 and 2C11 were the primary isozymes involved in the metabolism of atrazine in the rat (Hanioka et al. 1998a). However, further studies, also in rat liver microsomes, by the same group of investigators concluded that CYP1A1/2 is the main isozyme involved in the dealkylation of atrazine, and that CYP2B1/2 may be involved in hydroxylation of the isopropyl group (Hanioka et al. 1999).

Adams et al. (1990) examined the phase II portion of atrazine metabolism *in vitro* by incubating Sprague-Dawley and Fischer rat hepatic supernatant fractions (S-10) with [^{14}C]-atrazine and glutathione in a reaction mixture for 2 hours at 37 °C. Analysis of the products showed that phase I reactions proceeded more rapidly, with only 4% of the labeled metabolites recovered in the phase II portion. It was also noted that, in this *in vitro* system, most of the conjugated products were parent compound and not dealkylated metabolites. Phase II metabolism of atrazine was further demonstrated in another *in vitro* study that examined the activity of glutathione S-transferase (GST), the enzyme responsible for glutathione conjugation of atrazine, in cytosolic supernatants from Sprague-Dawley rats and Swiss-derived CD-1, C57BL/6, DBA/2, and Swiss-Webster mice (Egaas et al. 1995). Atrazine conjugates were detected in rats and in all strains of mice tested. These data support phase II metabolism of atrazine through glutathione conjugation and mercapturic acid formation.

While there are many similarities between and within species in phase I and phase II metabolism of atrazine, differences have also been noted. The products of phase I metabolism of atrazine have been shown to be qualitatively the same, but the rates of formation of the products and the ratio of the products was frequently different between species. Lang et al. (1996) found that the rate of formation of primary dealkylation products in human microsomes was up to 20-fold less than in rat microsomes, and the ratio of products was also different between humans, rats, and pigs. Hanioka et al. (1999) and Adams et al. (1990) found up to a 10-fold difference in rate of primary metabolite formation between rats, mice, guinea pigs, rabbits, pigs, sheep, goats, and chickens. There is also evidence of inter- and intra-species differences in phase II metabolism of atrazine. GST activity in rat liver cytosolic supernatants was much lower toward atrazine than in mice liver supernatants (about 6–37% of mouse activity) (Egaas et al. 1995). GST activity in female mouse supernatants was approximately 12–32% of that in males of the same strain, and remained constant between adolescence and sexual maturity (Egaas et al. 1995). In male mice, GST activity was much higher in the livers of sexually mature mice in all mouse strains tested except the C57BL/6, and was twice the level seen in adolescent mice of the CD-1 and Swiss-Webster strains.

3.4.4 Elimination and Excretion

Specific data on elimination and excretion of atrazine by any route were limited. However, the primary route of excretion appears to be in urine, as indicated by the detection of urinary atrazine and its metabolites in a number of species exposed via oral and dermal routes (Bakke et al. 1972; Buchholz et al. 1999; Catenacci et al. 1990, 1993; Meli et al. 1992; Timchalk et al. 1990). Fecal excretion was a minor route (Buchholz et al. 1999; Timchalk et al. 1990). No data were located regarding enterohepatic circulation and biliary secretion or excretion of atrazine in breast milk.

3.4.4.1 Inhalation Exposure

No studies were located regarding the elimination and excretion of atrazine following inhalation exposure in humans or animals.

3.4.4.2 Oral Exposure

No studies were located regarding the elimination and excretion of atrazine following oral exposure in humans.

Male F344 rats administered 30 mg/kg of [^{14}C]-atrazine by gavage eliminated 93% of the administered radioactivity within 72 hours (Timchalk et al. 1990). The primary route of excretion was in urine (67%); 36 and 21% of the administered radioactivity was eliminated in the 0–12- and 12–24-hour postexposure intervals, respectively. Fecal excretion accounted for 18% of the administered radioactivity. The elimination of atrazine from plasma followed first-order kinetics and the elimination half-life was calculated to be 10.8 hours (Timchalk et al. 1990). In rats that received a single dose of 50 mg/kg atrazine by gavage, atrazine and its metabolites were present in urine 24 hours postexposure and at 48 hours at a fraction of the 24-hour level (Meli et al. 1992).

3.4.4.3 Dermal Exposure

Doses of 0.167 mg (6.45 μCi) or 1.98 mg (24.7 μCi) of [^{14}C]-atrazine were applied to 25 cm^2 of the forearm of healthy males for 24 hours (Buchholz et al. 1999). Urinary excretion varied widely, accounting for 72, 30, and 3.5% of radioactivity absorbed by one low-dose and two high-dose individuals, respectively. Fecal excretion also varied, accounting for 11.5, 4.2, and 0%, respectively, of the absorbed radioactivity.

Urine was collected from six male workers at an atrazine production plant for 24 hours during and after an 8-hour workshift and analyzed for atrazine and atrazine metabolites (Catenacci et al. 1993). Fifty percent of the atrazine-related compound detected in the urine during the 24-hour period was excreted in the first 8 hours. A related study that measured only atrazine found that urinary levels were highest during and immediately after workshifts; levels 12 hours after the end of the workshift were one-tenth of the levels during the workshift (Catenacci et al. 1990).

3.4.4.4 Other Routes of Exposure

Lu et al. (1997b) examined the atrazine levels in the saliva of rats continuously infused with atrazine through a cannula in the femoral vein. Salivary rates were stimulated and controlled with intravenous injections of pilocarpine. Salivary and plasma levels of atrazine were simultaneously monitored over 200–300 minutes. Salivary atrazine levels remained relatively constant over a range of salivary flow rates, and the salivary/plasma concentration ratio remained fairly constant with changing salivary flow rates and plasma atrazine concentrations. The salivary atrazine concentration was found to be highly correlated with the plasma atrazine concentration.

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 3-2 shows a conceptualized representation of a PBPK model.

No PBPK models for atrazine were identified in the literature.

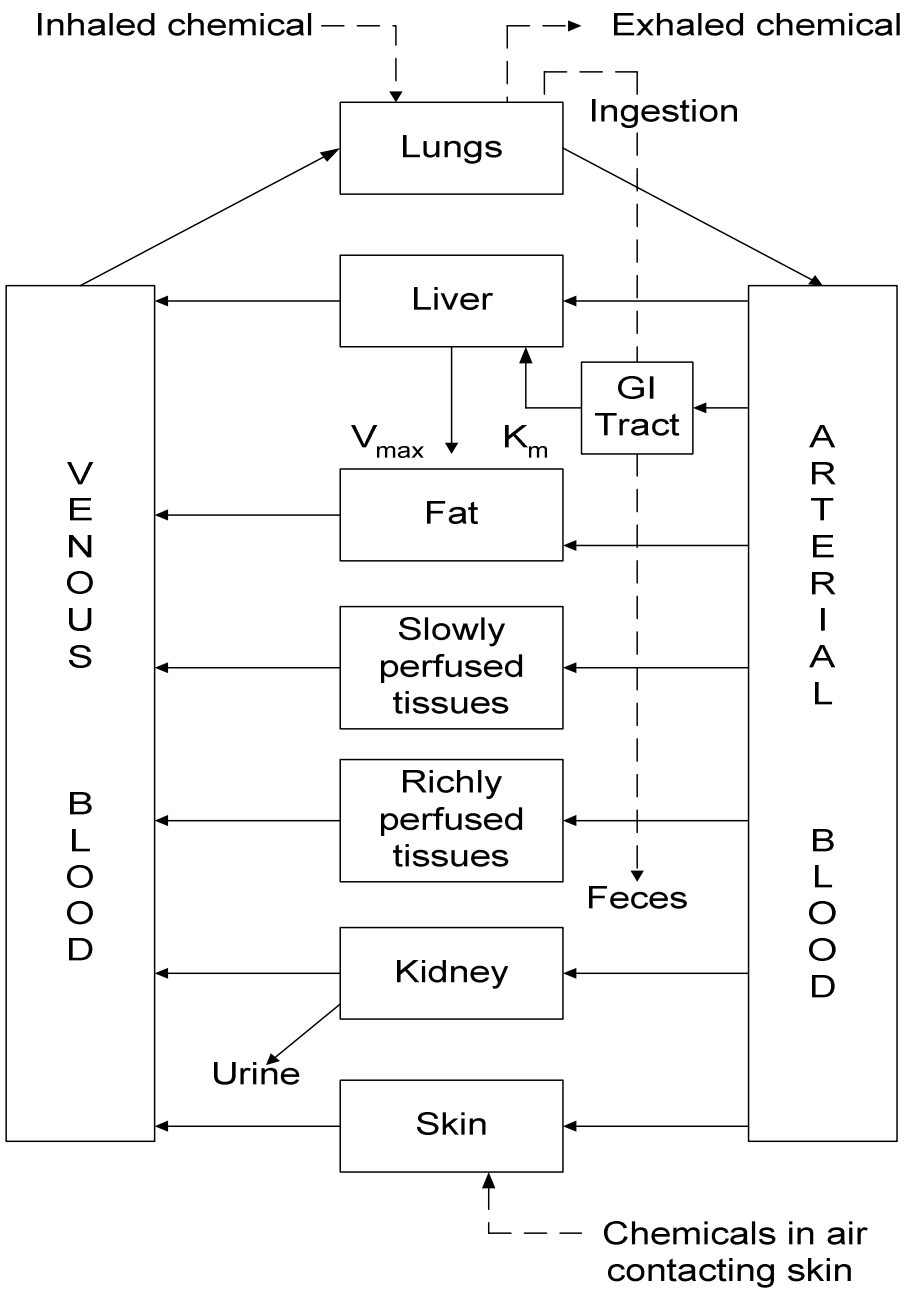
3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. No studies were located regarding the mechanism of absorption of atrazine in humans or animals by any route.

Atrazine is only slightly soluble in water, but has a fairly high solubility in *n*-octanol, with an octanol/water partition coefficient of 322 (Balke and Price 1988). Examination of the interaction of atrazine with 1,2-dipalmitoyl-3-*sn*-phosphatidylcholine (DPPC), a model for biological membranes,

Figure 3-2. 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.

showed that atrazine does not perturb the hydrophobic core of the lipid bilayer, but localizes superficially near the glycerol backbone (Tanfani et al. 1990). This does not seem to support passive diffusion through the gastrointestinal tract or skin.

Distribution. No studies were located regarding the mechanism of distribution of atrazine in humans or animals by any route.

Once absorbed, atrazine is transported throughout the body in the plasma (Timchalk et al. 1990). Atrazine has been detected in the kidney, small intestine, lung, liver, pancreas, muscle, heart, and plasma of a man who ingested weedkiller that contained atrazine (Pommery et al. 1993).

Metabolism. Atrazine is metabolized to its mono-dealkylated derivatives and to didealkylated atrazine in humans (Ademola et al. 1993; Buchholz et al. 1999; Catenacci et al. 1993) and animals (Bakke et al. 1972; Gojmerac and Kniewald 1989; Meli et al. 1992; Timchalk et al. 1990). *In vitro* studies using microsomal preparations from liver and other tissues of humans and animals have indicated that dealkylation of atrazine is mediated by cytochrome P-450 enzymes and requires NADPH (Adams et al. 1990; Ademola et al. 1993; Croce et al. 1996; Hanioka et al. 1998a, 1999; Lang et al. 1996, 1997; Meli et al. 1992; Venkatesh et al. 1992). Additional *in vitro* studies have indicated that CYP1A2, 2C19, and 1A1 may be the primary metabolic enzymes for atrazine in humans (Lang et al. 1997), while CYP2B1 and 2C11 may be the primary CYPs responsible for atrazine metabolism in rats (Hanioka et al. 1998a). Further studies concluded that CYP1A1/2 is the main isozyme involved in the alkylation of atrazine and that CYP2B1/2 may be involved in hydroxylation of the isopropyl group (Hanioka et al. 1999).

Atrazine also reportedly undergoes phase II metabolism, involving glutathione conjugation and conversion to mercapturic acid derivatives (Adams et al. 1990; Egaas et al. 1995).

Excretion. Atrazine is excreted as dealkylated and mercapturic acid derivatives primarily in the urine (Bakke et al. 1972; Buchholz et al. 1999; Catenacci et al. 1990, 1993; Meli et al. 1992; Timchalk et al. 1990), with feces being a minor route of excretion (Buchholz et al. 1999; Timchalk et al. 1990).

3.5.2 Mechanisms of Toxicity

The primary target of atrazine in some animal species is the female reproductive system Altered estrus cyclicity has been observed in Sprague-Dawley, Long-Evans, and Donryu rats following exposure to ≥5 mg/kg/day atrazine for intermediate or chronic durations (Aso et al. 2000; Cooper et al. 1996b; Eldridge et al. 1994a, 1999a; Wetzel et al. 1994) or to a single dose of 300 mg/kg/day (Cooper et al. 2000) and in pigs exposed to 1 mg/kg/day for 19 days (Gojmerac et al. 1999). These effects do not appear to be the result of intrinsic estrogenic activity of atrazine. Aso et al. (2000) found no increases in BrdU-positive (dividing) cells in the uterus of Sprague-Dawley, Long-Evans, or Donryu rats following 28 days of oral exposure to up to 50 mg/kg/day atrazine. Sprague-Dawley rats that received up to 300 mg/kg/day orally for 3 days had no increases in uterine weight, cytosolic progesterone receptor binding, or peroxidase activity; positive controls that received 17β-estradiol had increases in all three parameters (Connor et al. 1996). Tennant et al. (1994b) also found no increase in uterine weight in Sprague-Dawley rats exposed to 300 mg/kg/day for 3 days, supporting a lack of estrogenic activity. A recent set of experiments has indicated that atrazine may disrupt endocrine function, and the estrus cycle, primarily through its action on the central nervous system (Cooper et al. 2000) in a manner very similar to the known mechanism of reproductive senescence in some strains of rats. In certain strains of rats, including Sprague-Dawley and Long-Evans, reproductive senescence begins by 1 year of age, and results from inadequate stimulation of the pituitary by the hypothalamus to release LH; low serum levels of LH leads to anovulation, persistent high plasma levels of estrogen, and persistent estrus. Atrazine apparently accelerates the process of reproductive senescence in these strains of rats.

Atrazine has been shown to induce mammary tumor formation in female Sprague-Dawley rats, but not male Sprague-Dawley or male or female F344 rats (Stevens et al. 1994, 1999; Wetzel et al. 1994). This effect is also thought to be the result of acceleration of reproductive senescence, as described above. Both the failure to ovulate and the state of persistent estrus lead to constant elevated serum levels of endogenous estrogen, which may result in tumor formation in estrogen-sensitive tissues. Therefore, the mechanism of disruption of normal reproductive cyclicity and mammary carcinogenicity in these strains of rat likely does not involve direct interaction of atrazine with estrogen or the estrogen receptor. It also is probably not an adequate model for human reproductive toxicity or carcinogenicity because reproductive senescence in women involves ovarian depletion and decreased serum estrogen levels instead of decreasing hypothalamic function and increased serum estrogen levels (Carr 1992).

As previously stated, atrazine has been shown to alter serum luteinizing hormone (LH) and prolactin levels in Sprague-Dawley rats by altering the hypothalamic control of these hormones (Cooper et al. 2000). LH and prolactin are released from the pituitary in response to gonadotropin-releasing hormone (GnRH) from the hypothalamus, which is regulated by the interactions of various ligands with the gamma-aminobutyric acid receptor ($GABA_A$ receptor). Cooper et al. (1999) proposed that atrazine decreases the hypothalamic secretion of norepinephrine, which in turn decreases the release of GnRH. An alternate mechanism was proposed by Shafer et al. (1999) who examined the effect of atrazine and other triazine herbicides on $GABA_A$ receptors in cortical tissue from rat brain and found that atrazine can interfere with the binding of some ligands, but not others, to the $GABA_A$ receptor in a noncompetitive manner. The mono- and didealkylated atrazine metabolites had no effect on $GABA_A$ receptor binding. These preliminary data support the hypothesis that the hormonal effects of atrazine in Sprague-Dawley rats may be mediated through the $GABA_A$ receptor in the central nervous system. Although the effects of atrazine interaction with $GABA_A$ receptors on reproductive senescence may be peculiar to a few strains of rats, atrazine interaction with $GABA_A$ receptors may occur in other rat strains and in other species, including humans, with effects not yet realized. No data are currently available regarding this mechanism in humans.

Sanderson et al. (1999, 2000, 2001) has demonstrated that atrazine and its two primary metabolites, deethyl- and deisopropylatrazine, are capable of inducing aromatase (CYP19) activity, with a corresponding increase in aromatase ribonucleic acid (RNA), in the human adrenocortical carcinoma cell lines, JEG-3, H195R, and H295R. Aromatase is the rate-limiting enzyme in the conversion of androgens to estrogens, and its induction could play a role in estrogen-mediated pathologies. Atrazine has also been shown to alter the ratio of metabolites of estradiol in the estrogen receptor-positive (ER+) human breast cell line, MCF-7, although the results are conflicting (Bradlow et al. 1995; McDougal and Safe 1998; Sanderson et al. 2001). Estradiol metabolism proceeds via hydroxylation at one of two mutually exclusive carbons, C-2 or C-16α. The C-2 product, 2-OHE_1, is much less potent than estradiol (and may even be anti-estrogenic) and is nongenotoxic. The C-16α product, 16α-OHE_1, is a fully potent estrogen that is genotoxic, tumorigenic, and causes increased cell proliferation by covalently binding to estrogen receptors and interacting with deoxyribonucleic acid (DNA). McDougal and Safe (1998) reported a slight decrease, compared to controls, in the ratio of 16α-OHE_1/2-OHE_1 in MCF-7 cells incubated with atrazine, while Bradlow et al. (1995) reported that the ratio of 16α-OHE_1/2-OHE_1 in MCF-7 cells incubated with atrazine was approximately 12 times that of untreated control cells, and was several times that of cells treated with DMBA, a known carcinogen. Atrazine caused both a decrease in the amount of 2-OHE_1 and an increase in the amount of 16α-OHE_1. This study suggests that atrazine could play a role in cancer

development in estrogen-responsive tissues, since studies have shown that an elevated 16α-OHE_1/2-OHE_1 ratio is associated with breast and other cancers in animals (Bradlow et al. 1995; Telang et al. 1992). In similar experiments using the ER^- cell lines, MDA-MB-231 and MCF-10, no inhibitory or stimulatory changes in estrogen metabolism were seen (Bradlow et al. 1997). This suggests that ER status of cells plays a role in the ability of atrazine to cause changes that might result in cancer of estrogen-responsive tissues. It has been speculated that two response elements in the DNA of these cells, one requiring the xenobiotic (atrazine) and one requiring an ER-ligand complex, must be activated in order to initiate an increase in expression of the cytochrome P-450 enzyme responsible for 16α-hydroxylation of estrogen (Bradlow et al. 1997).

Atrazine may also interfere with male hormone regulation and activity. Testosterone conversion to its primary metabolite, 5α-dihydroxytestosterone (5α-DHT), was significantly decreased in rat prostate tissue exposed to 0.465–1.392 µmol atrazine for 3 hours (Kniewald et al. 1995). Additionally, the number of receptor binding sites for 5α-DHT was reduced in prostate homogenates from rats that had received 60 or 120 mg/kg/day atrazine orally for 7 days (Kniewald et al. 1995; Šimić et al. 1994). These effects are reversible upon cessation of atrazine exposure, although recovery in prepubescent rats was slower than in adult rats. Leydig cell testosterone production was directly inhibited by *in vitro* exposure to atrazine in isolated rat cells (Friedmann 2002). A detailed mechanism for these effects has not been elucidated.

3.5.3 Animal-to-Human Extrapolations

The most sensitive target of atrazine toxicity in animals is the reproductive system. A number of studies have shown a delay in the onset of estrus in pigs exposed to 1–2 mg/kg/day (Gojmerac et al. 1996, 1999) and altered estrus cyclicity and plasma hormone levels in rats exposed to 7–300 mg/kg/day; some rat strains, especially Sprague-Dawley and Long-Evans, appear to be more sensitive to these effects (Cooper et al. 1996b, 2000; Eldridge et al. 1994a, 1999a; Šimić et al. 1994; Wetzel et al. 1994). These effects are not likely to be mediated by estrogenic activity of atrazine since it has been shown that atrazine does not bind to estrogen receptors *in vitro* or induce uterine decidualization in rats (Aso et al. 2000; Connor et al. 1996; Tennant et al. 1994b). There is some evidence that the estrus cycle effects are the disruption of the gonadal-hypothalamic-pituitary axis, which results in lower GnRH release from the hypothalamus and, ultimately, lack of ovulation increased plasma estradiol levels, and persistent estrus (Cooper et al. 2000). Strains that normally experience reproductive senescence via the same mechanism are more likely to experience estrus disruption in response to atrazine. However, reproductive senescence in humans is

characterized by ovarian depletion and decreased estrogen levels, making it unlikely that effects similar to the estrus effects seen in rats would occur in humans. Therefore, the rat does not appear to be an appropriate model for this end point. Shafer et al. (1999) has demonstrated (*in vitro*) that atrazine can inhibit the binding of some, but not all, ligands to the GABA receptor. The GABA receptor-ligand complex acts on $GABA_A$ chloride channels in the hypothalamus, stimulating the release of GnRH. Inhibition of ligand binding to GABA receptors could contribute to the disruption of the estrus cycle in rats, although this has not been demonstrated *in vivo*. The GABA receptor has many isomeric forms with diverse pharmacology. It is possible that atrazine could interact with the GABA receptor(s) in other species, including humans, with different effects.

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).

There is considerable evidence that atrazine interferes with the normal function of the endocrine system. Increases in pituitary gland weight and enlarged pituitaries have been observed in male and female rats exposed to 12 mg/kg/day atrazine and higher for acute, intermediate, and chronic durations (Babic-Gojmerac et al. 1989; EPA 1984f, 1987d; Šimić et al. 1994). Significant decreases in pituitary hormones have also been observed. Decreases in prolactin and luteinizing hormone levels have been observed in rats exposed for 1, 3, or 21 days (Cooper et al. 2000) or 9 months (Wetzel et al. 1994).

In the reproductive system, these alterations in pituitary hormone levels sometimes result in significant alterations in blood estradiol and progesterone levels (Cooper et al. 1996b; Eldridge et al. 1994a; Wetzel et al. 1994). Whether these hormone levels are increased or decreased appears to be strain specific in rats, as well as age-related. The alterations in estradiol and progesterone levels can affect estrus cyclicity. Disruption of the percentage of days in estrus or diestrus has been observed in Long Evans and Sprague-Dawley rats (Cooper et al. 1996b, 2000; Eldridge et al. 1994a; Wetzel et al. 1994). Acute and chronic atrazine exposure to peripubertal male rats was associated with decreased serum and intratesticular testosterone levels and lutenizing hormone concentrations (Friedmann 2002; Trentacoste et al. 2001). Leydig cell testosterone production was directly inhibited by *in vitro* exposure to atrazine in isolated rat cells (Friedmann 2002).

The toxicity of atrazine to the pituitary has also resulted in developmental effects. When rat dams were exposed to atrazine during lactational days 1–4, atrazine suppressed the prolactin surge, which is usually induced by pup suckling. The resultant decreased prolactin levels in breast milk resulted in prostate inflammation in the adult offspring (Stoker et al. 1999).

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).

There is no direct information on the toxicity of atrazine in children and no information on effects in adults who were exposed as children. A single cohort study of farm couples in Canada indicated that atrazine exposure may be associated with increased preterm delivery and miscarriage (Arbuckle et al. 2001; Savitz et al. 1997), and an ecological study indicated that atrazine levels in drinking water were positively associated with decreased intrauterine growth rates and increased birth defects in the respective communities (Munger et al. 1992b, 1997).

Animal data indicate that the primary target of atrazine is the reproductive system and that atrazine can affect adult animals, which may result in effects in the offspring. Male rats exposed to 25, but not 12.5, mg/kg/day atrazine via lactation on postpartum days 1–4 had inflammation of the lateral prostate at 120 days of age (Stoker et al. 1999). This effect was thought to be the result of a lack of prolactin release in the dam in response to pup suckling, which was verified by monitoring plasma prolactin levels during and after pup suckling. Also, co-administration of ovine prolactin with atrazine to the dam eliminated the increase in prostate inflammation in offspring. Prolactin plays an important role in the postnatal development of the tuberoinfundibular dopaminergic (TIDA) system, which, in the adult rat, has an inhibitory effect on prolactin release from the pituitary (Shyr et al. 1986). A lack of prolactin during development results in a lack of prolactin release control and hyperprolactinemia in the adult rats, which leads to lateral prostate inflammation (Tangbanluekal and Robinette 1993).

Peruzović et al. (1995) found subtle neurobehavioral effects (increased spontaneous activity in females and increased performance in avoidance conditioning trials in males) in offspring of rat dams exposed to 120 mg/kg atrazine 6 times during a 12-day period that ended 4 weeks before the rats were bred. The mechanism for this effect is unknown, but since atrazine is not thought to persist in tissues, it may be mediated through changes in the dam that later affect the offspring. These data indicate that the developing organism may be susceptible to the effects of atrazine and/or its metabolites.

There are no studies that indicate that metabolism of atrazine differs between children and adults or between young and adult animals. The primary pathway by which atrazine is metabolized is dealkylation

to yield the mono- and/or didealkylated atrazine derivatives. *In vitro* studies with human liver microsomes and recombinant cytochrome P-450 (CYP) isozymes indicate that multiple CYP isozymes are probably involved in the dealkylation of atrazine in humans (Lang et al. 1997). This study indicates that CYP1A2, CYP2C19, and CYP1A1 may be the major CYP enzymes for atrazine, but that other forms, including CYP2A6, CYP2C9, and CYP2B6, are likely to be major contributors, especially in individuals with low levels of CYP2C19 or CYP1A2. While CYP2C19 and CYP1A2 are not present in appreciable levels in human fetal liver, their activities increase to adult levels by 4–6 months of age (Leeder and Kearns 1997; Ratenasavanh et al. 1991; Sonnier and Cresteil 1998). These data indicate that infants, at or shortly after birth, are capable of metabolizing atrazine to its dealkylated metabolites.

An association was found between Iowa communities exposed to an average of 2.2 µg/L atrazine in the drinking water in 1984–1990 and an increased risk of intrauterine growth retardation and cardiac, urogenital, and limb reduction defects (Munger et al. 1992b, 1997).

No data were located regarding the passage of atrazine or its metabolites across the placenta or its excretion in breast milk.

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 atrazine 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 atrazine 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 Atrazine

Atrazine is primarily excreted in the urine as dealkylated metabolites and mercapturic acid derivatives (Bakke et al. 1972; Buchholz et al. 1999; Catenacci et al. 1993; Gojmerac and Kniewald 1989; Meli et al. 1992; Timchalk et al. 1990), which can be detected in urine at levels as low as 1 µg/L (Ikonen et al. 1988). Atrazine derivatives, especially the mercapturic acid derivatives, are useful biomarkers of exposure (Jaeger et al. 1998; Lucas et al. 1993); however, atrazine is eliminated from the body in 24–48 hours (Catenacci et al. 1990; Meli et al. 1992; Timchalk et al. 1990) and thus, the tests must be performed soon after the exposure. Atrazine and its metabolites can also be detected in blood and tissues at levels as low as 14.25 ng/g (Pommery et al. 1993). The detection of atrazine in urine or tissues may be a specific biomarker for atrazine exposure, but <2% of atrazine is excreted in the urine unchanged (Buchholz et al. 1999; Catenacci et al. 1993). The detection of atrazine metabolites is not specific for atrazine exposure, but may also be a biomarker of exposure to other triazine herbicides such as cyprazine,

simazine, or propazine (Bradway and Moseman 1982; Hanioka et al. 1999; Larsen and Bakke 1975). Analysis for dealkylated metabolites should be performed soon after sample collection because they can degrade over time and during freezing and thawing (Bradway and Moseman 1982); mercapturic acid derivatives may provide a more reliable biomarker (Jaeger et al. 1998; Lucas et al. 1993). There is no quantitative relationship between exposure levels and levels of atrazine or metabolites found in the body (Lucas et al. 1993). Some of the analytical methods used to detect atrazine in biological samples are provided in Table 7-1.

A pair of studies by Lu et al. (1997a, 1998) measured the levels of atrazine in saliva in rats under different blood concentrations of atrazine (regulated by intravenous infusion) and different salivary flow rates (controlled by administration of pilocarpine) and found that salivary atrazine levels reflected the levels of free atrazine in the plasma. No attempt was made to measure atrazine metabolites. Salivary levels of atrazine may be a convenient way to determine exposure, but have not been shown to be quantitatively related to oral or dermal exposure levels.

3.8.2 Biomarkers Used to Characterize Effects Caused by Atrazine

The primary target organs of atrazine are the female reproductive system and the liver. The reproductive effects in animals included altered estrus cyclicity or anestrus (Cooper et al. 1996b, 2000; Ćurić et al. 1999; Eldridge et al. 1994a, 1999a; Gojmerac et al. 1996, 1999; Šimić et al. 1994; Wetzel et al. 1994), altered serum and/or pituitary hormone levels (Cooper et al. 1996b; Eldridge et al. 1994a; Gojmerac et al. 1996, 1999), reduced fecundity (Šimić et al. 1994), increased litter resorption (Narotsky et al. 2001), decreased ovarian and uterine weights (Ashby et al. 2002; Eldridge et al. 1994a), and ovarian histopathology (Ćurić et al. 1999; Gojmerac et al. 1996). The hepatic effects seen following atrazine exposure were increased serum lipids and liver enzymes (Gojmerac et al. 1995; Islam et al. 2002; Morichetti et al. 1992; Radovcic et al. 1978; Santa Maria et al. 1987; Wurth et al. 1982), liver histopathology (Ćurić et al. 1999; Gojmerac et al. 1995), changes in liver weight (Aso et al. 2000; EPA 1984f, 1987d, 1987f), and changes in trigycerides and globulin levels (EPA 1984f, 1987d). While all of these effects may be useful biomarkers to indicate possible atrazine exposure, none are specific for atrazine. Additionally, it is unclear which, if any, of the above reproductive effects may be caused by atrazine exposure in humans.

3.9 INTERACTIONS WITH OTHER CHEMICALS

No data were located regarding interactions of atrazine with other chemicals in humans. Ugazio et al. (1991a, 1991b, 1993) examined the effects of atrazine on hexabarbital-induced sleep time (HB-ST) in rats. Atrazine exposure consistently reduced HB-ST, especially in males, indicating an induction of microsomal enzymes (Ugazio et al. 1991a). In offspring of treated animals, which received atrazine via lactation and then directly following weaning, HB-ST was also shortened, most notably at weaning (21 days of age). Induction of enzymes was verified by determination of liver microsomal protein concentrations and metabolic enzyme activities in male rats; all were elevated significantly at weaning only, and elevated without statistical significance thereafter (Ugazio et al. 1991a). A single dose of atrazine to Wistar rats also reduced HB-ST and elevated some metabolic enzymes, and atrazine co-administered with carbon tetrachloride (CCl_4) attenuated the effects of CCl_4 (Ugazio et al. 1993). Therefore, atrazine may alter the effects of other chemicals via the induction of metabolic enzymes in the liver.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

Atrazine has been shown to cause liver effects in animals; therefore, people with liver damage or disease may be at greater risk from exposure to atrazine. No further information was located that identified any human population that is unusually susceptible to the toxicity of atrazine. See Section 3.7 for a discussion on children's susceptibility.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

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

Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. 2nd ed. Baltimore: Williams & Wilkins.

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

Data regarding the reduction of atrazine absorption in humans after inhalation exposure were not located. Oral absorption of atrazine can be reduced with gastric lavage, activated charcoal, sodium sulfate, and cathartics (Ellenhorn et al. 1997; Haddad et al. 1998). Since many commercial formulations of organochlorine insecticides contain organic solvents, emesis is not usually recommended due to the hazard of solvent aspiration (Ellenhorn et al. 1997). In addition, oils should usually not be used as cathartics since they may enhance the absorption of atrazine (Haddad et al. 1998).

Dermal absorption of atrazine can be reduced by removing contaminated clothing and thoroughly washing the exposed skin with a mild soap (Ellenhorn et al. 1997; Haddad et al. 1998). Oils should not be used as a cleansing agent since they may facilitate dermal absorption (Haddad et al. 1998).

3.11.2 Reducing Body Burden

No experimental data regarding methods for reducing the atrazine body burden were located. Since animal studies indicate that atrazine is rapidly metabolized and cleared from the body, methods for reducing body burden are not expected to be especially effective in reducing human exposures.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

No reports of methods that would interfere with the mechanism of atrazine toxicity were identified.

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 atrazine 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 atrazine.

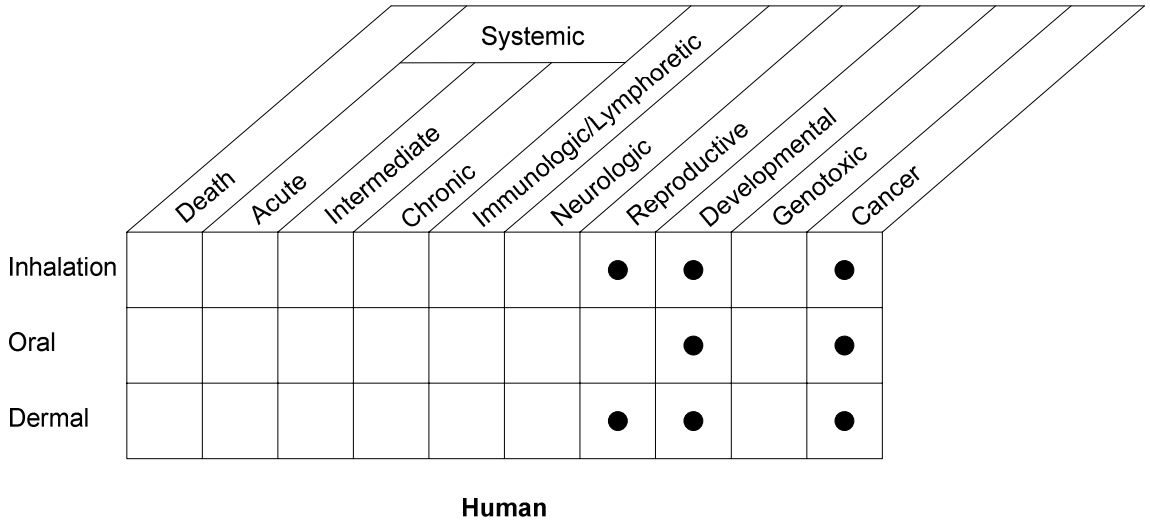
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

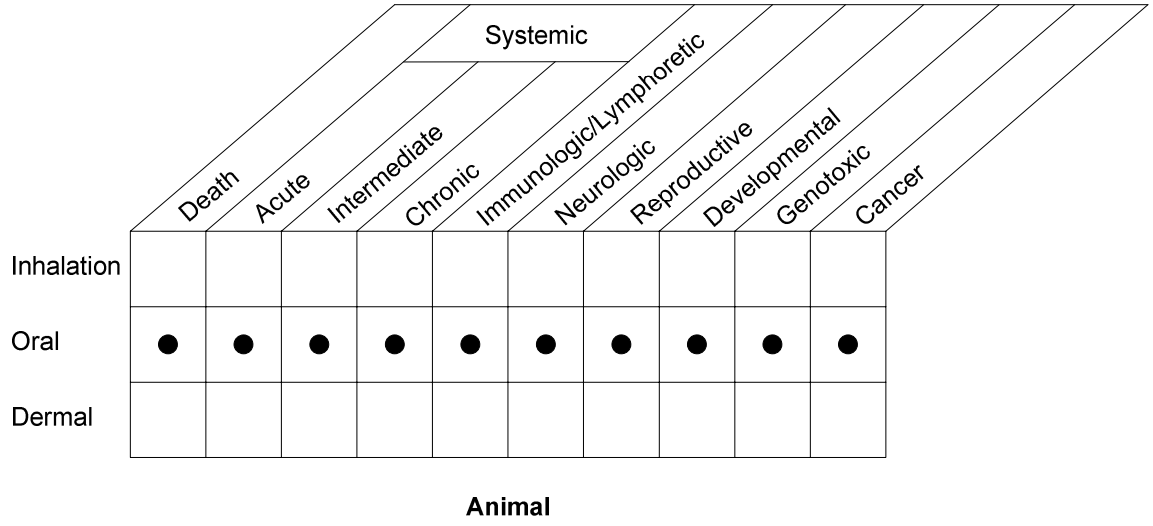
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to atrazine are summarized in Figure 3-3. The purpose of this figure is to illustrate the existing information concerning the health effects of atrazine. Each dot in the figure indicates that one or more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

There are limited data on the toxicity of atrazine in humans. The available ecological studies examined the potential of atrazine to induce reproductive and developmental effects and cancer. Two case reports discuss the lethality of atrazine and its toxic effect to the skin.

Figure 3-3. Existing Information on Health Effects of Atrazine



Human



Animal

● Existing Studies

The database for health effects of atrazine in laboratory animals is limited to oral studies, as can be seen in Figure 3-3. These studies have examined lethality, systemic, reproductive, and developmental toxicity, and carcinogenicity. Although some studies have examined the immunotoxicity and neurotoxicity of atrazine, these potential effects have not been thoroughly investigated. Genotoxicity data on atrazine are available from both *in vitro* and *in vivo* studies.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. The only human data on the acute toxicity of atrazine are two case reports, which describe the lethality (Pommery et al. 1993) and the dermal toxicity (Schlicher and Beat 1972). Because each report only described one individual, interpretation of the study is limited. Studies in laboratory animals are limited to oral exposure. Acute-duration oral studies in animals primarily focused on the endocrine and reproductive toxicity of the compound. These studies reported alterations in pituitary weight or size (Babic-Gojmerac et al. 1989; Šimić et al. 1994), thyroid gland histology and thyroid hormone levels (Kornilovskaya et al. 1996), pituitary hormone levels (Cooper et al. 2000), and effects on the estrus cycle (Cooper et al. 2000; Šimić et al. 1994). An MRL of 0.01 mg/kg/day has been derived for acute-duration oral exposure to atrazine based on a NOAEL of 1 mg/kg/day for decreased body weight gain in pregnant rabbits exposed to atrazine on gestational days 7–19 (Infurna et al. 1988). The developmental toxicity of atrazine has also been investigated in several studies that found profound maternal toxicity in rats and rabbits (Infurna et al. 1988), less severe skeletal effects (incomplete ossification) (Infurna et al. 1988), prostatitis in male offsprings (Stoker et al. 1999), and neurodevelopmental effects (Peruzović et al. 1995). With the exception of endocrine and body weight effects, most of the acute-duration studies did not examine for systemic effects. A study by Santa Maria et al. (1987) did report renal and hepatic effects. Additional oral studies are needed to establish dose-response relationships for effects on the endocrine system, which appears to be the most sensitive target of toxicity. Inhalation and dermal exposure studies are needed to identify the critical effect for these routes and establish dose-response relationships.

Intermediate-Duration Exposure. No human studies involving intermediate-duration exposure to atrazine were located. Additionally, no animal inhalation or dermal exposure studies were identified. As with acute toxicity, the intermediate-duration studies primarily focused on the ability of atrazine to disrupt the endocrine system and alter the estrus cycle. A number of studies have examined hormone levels and

the estrus cycle in several strains of rats exposed to atrazine (Aso et al. 2000; Cooper et al. 2000; Eldridge et al. 1994a; Wetzel et al. 1994). These studies also reported decreases in body weight gain. Studies in pigs (Ćurić et al. 1999; Gojmerac et al. 1995, 1996, 1999) have examined reproductive and systemic end points and reported very low LOAEL values. An intermediate-duration oral MRL of 0.003 mg/kg/day has been derived based on a LOAEL from a 19-day study in which pigs that were administered 1 mg/kg/day atrazine in the diet had a delayed onset of estrus (Gojmerac et al. 1999). None of the other available studies examined a wide range of potential systemic effects. Additional oral studies that examine the potential systemic toxicity of atrazine are needed. Inhalation and dermal exposure studies are also needed to identify critical effects and establish dose-response relationships.

Chronic-Duration Exposure and Cancer. Human studies designed to assess the reproductive toxicity (Arbuckle et al. 2001; Curtis et al. 1999; Savitz et al. 1997) following dermal and inhalation exposure and developmental toxicity following oral exposure (Munger et al. 1992b, 1997) have been identified. Several studies have investigated the chronic toxicity of atrazine following oral exposure of laboratory animals. Studies in rats (EPA 1984f, 1987d) and dogs (EPA 1987f) have reported decreased erythrocyte parameters, liver effects, functional impairment of the kidney (rats only), cardiac effects (dogs only), endocrine effects (enlarged pituitary and increased adrenal gland weight; rats only), and decreased body weight gain. The reproductive toxicity of atrazine has also been investigated in rats (Narotsky et al. 2001; Trentacoste et al. 2001; Wetzel et al. 1994). Several mild to moderate endocrine effects have been observed in laboratory animals following atrazine administration, the majority of which are related to reproductive effects. The endocrine effects consisted of alterations in gland weight (Babic-Gojmerac et al. 1989; Eldridge et al. 1994a; EPA 1984f, 1987d; Šimić et al. 1994; Vos et al. 1983), histological damage in some endocrine glands (Kornilovskaya et al. 1996), and alterations in hormone levels (Babic-Gojmerac et al. 1989; Cooper et al. 2000; Cummings et al. 2000b; Eldridge et al. 1994a; Friedmann 2002; Kornilovskaya et al. 1996; Stoker et al. 1999; Trentacoste et al. 2001; Wetzel et al. 1994). The existing database on the chronic-duration oral toxicity of atrazine was considered inadequate for MRL derivation. Additional studies that further define the dose-response relationships for the most sensitive end points, particularly reproductive toxicity, would be useful. Inhalation and dermal exposure studies are needed to identify critical effects and establish dose-response relationships.

A study of residents consuming drinking water contaminated with atrazine found a significant association between atrazine levels and increased risk of stomach cancer and decreased risk of colon cancer (Van Leeuwen et al. 1999). Several ecological and population-based case-control studies of pesticide use by farmers by both inhalation and dermal exposures have shown possible associations between atrazine

exposure and brain, testis, and prostate cancers (Mills 1998), leukemia (Mills 1998), and increased incidence of non-Hodgkin's lymphoma (Weisenburger 1990; Zahm 1993b). No significant increases were found, however, in the incidence of multiple myeloma (Brown et al. 1993), non-Hodgkin's lymphoma (Cantor et al. 1992), or leukemia (Brown et al. 1990) in male farmers exposed to atrazine. No association was found between oral atrazine exposure and the incidence of breast or ovarian cancer in Kentucky women (Hopenhayn-Rich et al. 2002). Although limitations of these studies include lack of specific exposure data, recall error, and exposure to chemicals other than atrazine, some of these studies nevertheless provide suggestive evidence of an association between atrazine and some forms of cancer in humans.

Available carcinogenicity data in animals suggest that high doses atrazine in the diet resulted in an increased incidence and earlier onset of mammary tumors in female Sprague-Dawley rats as compared to age-matched controls (Stevens et al. 1994, 1999; Wetzel et al. 1994); these effects were not found in similarly exposed F344 rats (Pintér et al. 1990; Wetzel et al. 1994) or CD-1 mice (Innes et al. 1969; Stevens et al. 1999). Additional carcinogenicity studies by the inhalation, oral, and dermal routes would be useful for better assess the carcinogenic potential of atrazine and determining whether the carcinogenic effects observed in female Sprague-Dawley rats are relevant to humans.

Genotoxicity. The available genotoxicity data indicate that atrazine may have genotoxic potential. *In vivo* genotoxicity studies have found increases in DNA strand breaks (Pino et al. 1988), micronucleus formation (Gebel et al. 1997; Kligerman et al. 2000b), an increase of DNA damage in leukocytes, as measured by tail moment (Tennant et al. 2001) in mice, somatic mutations (Torres et al. 1992; Tripathy et al. 1993), dominant lethal mutations (Murnick and Nash 1977), and aneuploidy (Murnick and Nash 1977) in *Drosophila melanogaster*. In *in vitro* assays using human lymphocytes, atrazine induced DNA damage (Ribas et al. 1995) and chromosomal aberrations (Meisner et al. 1992, 1993). In general, genotoxic potential was not detected in assays using *S. typhimurium* (Adler 1980; Andersen et al. 1972; Bartsch et al. 1980; Butler and Hoagland 1989; Kappas 1988; Lusby et al. 1979; Morichetti et al. 1992; Ruiz and Marzin 1997; Seiler 1973; Sumner et al. 1984; Zeiger et al. 1988), *E. coli* (Adler 1980; Ruiz and Marzin 1997), or bacteriophages (Andersen et al. 1972). In contrast, studies for gene mutations (Emnova et al. 1987; Mathias et al. 1989; Morichetti et al. 1992; Plewa and Gentile 1976), mitotic recombination (Adler 1980), anaeuploidy (Benigni et al. 1979), and micronucleus formation (Mohammed and Ma 1999) in yeast have been positive. There have been conflicting results in studies concerning the genotoxicity of atrazine to human lymphocytes. In human lymphocytes, an increase in DNA damage was observed (Ribas et al. 1995); a later study by this group (Ribas et al. 1998) did not confirm this finding. Meisner et

al. (1992, 1993) and Lioi et al. (1998) observed increased chromosomal aberrations in human lymphocytes, while Kligerman et al. (2000a) and Ghiazza et al. (1984) did not observe any significant increases in the occurrence of chromosomal aberrations. The occurrences of sister chromatid exchange in human lymphocyte cells were not found to be altered in several studies (Dunkelberg et al. 1994; Kligerman et al. 2000a; Ribas et al. 1998); in contrast, Lioi et al. (1998) did observe increased sister chromatid exchange. The small number of *in vivo* genotoxicity studies and the apparent conflict between prokaryotic and eukaryotic genotoxicity assay suggest that additional information is needed to assess the genotoxicity of atrazine.

Reproductive Toxicity. The reproductive toxicity of atrazine has been examined in humans exposed via inhalation and dermal exposure and in orally exposed animals. In studies of couples living on farms using atrazine, a significant association between herbicide activity and increase in preterm deliveries was seen (Savitz et al. 1997). Savitz et al. (1997) found no association with atrazine use and the risk of miscarriage; however, Arbuckle et al. (2001) did find a moderate increase in risk of spontaneous abortion, during the first 20 weeks of conception, in women who were exposed to atrazine 3 months prior and up to 1 month of conception. No association was found between atrazine use and decreased fecundity (Curtis et al. 1999). Oral exposure studies in rats and pigs have demonstrated that atrazine is a reproductive toxicant. In pigs, a decrease in serum estrogen levels, increase in serum progesterone levels, multiple ovarian follicular cysts, persisting corpus luteum, cystic degeneration of secondary follicles, and a short-term delay in estrus onset were observed (Ćurić et al. 1999; Gojmerac et al. 1996, 1999). The intermediate-duration oral MRL for atrazine was based on the LOAEL for delayed onset of estrus identified in the Gojmerac et al. (1999) pig study. In rats, alterations in estrus cycle (Aso et al. 2000; Cooper et al. 1996b; Eldridge et al. 1994a; Šimić et al. 1994; Wetzel et al. 1994), impaired fertility when exposed females were mated with exposed or unexposed males (Šimić et al. 1994), litter resorption (Narotsky et al. 2001), delayed vaginal opening, and decreased uterine and ovarian weights (Ashby et al. 2002; Eldridge et al. 1994a), and decreased serum estradiol levels (Cooper et al. 2000; Eldridge et al. 1994a) were observed. Many of the rat studies tested several rat strains and found significant strain differences. For example, an increase in the number of days in estrus was found in Sprague-Dawley rats, but in F344 rats, there was a decrease in the percentage of number of days in estrus and an increase in the percentage of days in diestrus (Aso et al. 2000). F344 rats were found to be more susceptible than Sprague-Dawley and Long Evans rats to atrazine-induced pregnancy loss (Narotsky et al. 2001).

The rat studies found substantial strain differences and it is not known which rat strain, if any, would be an appropriate model for human reproductive toxicity. Additional studies are needed to address the

apparent strain difference. Reproductive toxicity studies in other species would also address the issue of a model for human reproductive toxicity. The studies by Šimić et al. (1994), in which treated males were mated with untreated females, and the rat 2-generation (EPA 1987e) study are the only available studies that attempted to assess male reproductive toxicity. Šimić et al. (1994) observed a decrease in the number of sperm positive females when atrazine-exposed male and female rats were mated; no effect was seen when exposed males were mated with unexposed females and only a slight effect (82% sperm positive versus 100% in controls) was seen when exposed females were mated with unexposed males. EPA (1987e) found no significant alterations in fertility in a 2-generation rat study in which male and female Charles River albino rats were fed 27 mg/kg/day atrazine for at least 10 weeks prior to mating. Additional studies are needed to assess whether the testes is also a sensitive target of atrazine toxicity.

Developmental Toxicity. There are limited data on the developmental toxicity of atrazine in humans. The results of a survey of 1,898 farm couples living year-round on farms in Ontario, Canada, designed to assess reproductive effects of pesticides, indicated that the sex ratio was not altered and the risk of small for gestational age deliveries was not increased in relation to pesticide exposure (atrazine exposure level not available) (Savitz et al. 1997). It is probable that the pesticide application resulted in both dermal and inhalation exposure. Significant increases in the risk of intrauterine growth retardation and other birth defects were found in a community drinking water contaminated with atrazine (Munger et al. 1992b, 1997). As with most ecological studies, these studies cannot establish a strong causal relationship between developmental effects and atrazine exposure. Developmental toxicity studies in animals are limited to the oral route. In studies of rats (Crl:COBS CD [SD] BR, Sprague-Dawley, F344, and Long Evans) and rabbits (New Zealand White) exposed to atrazine during gestation, an increase in resorptions and postimplantation loss was observed in rats, and increases in resorptions, and postimplantation losses, and decreases in live fetuses and fetal body weight were observed in rabbits (Infurna et al. 1988; Narotsky et al. 2001). However, these fetal effects were accompanied by severe maternal body weight loss and general toxicity. Thus, it is not known if the effects were due to direct toxicity of atrazine to the fetuses or due to atrazine-induced maternal toxicity. For the rats, less severe fetal effects (decreased fetal body weight, incomplete ossification) were observed at the next lowest dose tested and were not associated with severe maternal toxicity. The Infurna et al. (1988) study suggests that the rabbit may be more sensitive that the rat to the toxicity of atrazine, identifying a serious LOAEL at almost the same dose level as a less serious LOAEL in the rat study. Studies investigating the effect of peripubertal exposure to atrazine on the reproductive development of female rats found an association with atrazine exposure and delayed vaginal opening and altered estrus cycles (Ashby et al. 2002; Laws et al. 2000) and delayed uterine growth (Ashby et al. 2002). Additional developmental toxicity studies are

needed to assess the apparent species differences in developmental toxicity. Rat studies also demonstrated that pregestational exposure to atrazine can result in neurodevelopmental effects in the offspring (Peruzović et al. 1995) and lactational exposure can result in inflammation of the lateral prostate in adult male offspring (Stoker et al. 1999). Additional studies, particularly studies that examine the offspring as they mature, are needed to further elucidate these effects.

Immunotoxicity. No human studies examining the immunotoxicity of atrazine were located. Oral exposure studies in mice, rats, and pigs suggest that the immune system may be a target of atrazine toxicity. Decreases in thymus weight (Líšková et al. 2000; Vos et al. 1983) and increases in thyroid and mesenteric lymph node weights (Vos et al. 1983) were observed in mice (Líšková et al. 2000) and rats (Vos et al. 1983); lymphoid depletion in the lymphoid follicles of the prescapular and mesenteric lymph nodes were observed in pigs (Ćurić et al. 1999). The study by Líšková et al. (2000) also included some tests of immune function. Significant alterations in humoral immunity were observed, but no changes in cell-mediated immunity or autoimmunity were found. Additional studies are needed to assess the immunotoxicity of atrazine; a study performing an immunological battery of tests would provide valuable information on the potential of atrazine to impair immune function.

Neurotoxicity. No human data on the neurotoxic potential of atrazine were located. The available data come from two acute-duration oral studies in rats (Bainova et al. 1979; Podda et al. 1997) and an intermediate-duration study in rats (Dési 1983). The acute-duration studies found alterations in cerebellar activity in rats exposed to a moderate dose of atrazine. The intermediate-duration study, tested a slightly lower dose, did not find any differences in a behavioral maze test. These data support the finding of neurodevelopmental effects in the offspring following pregestational exposure (Peruzović et al. 1995). A neurotoxicity battery is recommended to provide additional information on the neurotoxicity of orally-administered atrazine. Neurotoxicity should also be tested by the inhalation and dermal routes of exposure.

Epidemiological and Human Dosimetry Studies. Limited human cohort and ecological studies have been performed and generally involved exposure to more than one pesticide at poorly-characterized levels during the period of time examined. The primary end points examined included reproductive (Arbuckle et al. 2001; Curtis et al. 1999; Savitz et al. 1997), developmental (Munger et al. 1992b, 1997), and cancer (Brown et al. 1990, 1993; Cantor et al. 1992; Hopenhayn-Rich et al. 2002; Mills 1998; Van Leeuwen et al. 1999; Weisenburger 1990; Zahm et al. 1993a, 1993b).

Studies of people occupationally exposed to only atrazine (no other pesticides) would be valuable in assessing the effects of atrazine on human health. Since one of the most significant effects in animals is disruption of estrus cyclicity, epidemiology studies of reproductive parameters in humans exposed to atrazine would be particularly relevant. Such studies would be most valuable if dosimetry methods could be developed to provide reliable exposure data to accompany health effects data. This would assist in establishing cause/effect relationships and in developing methods to monitor individuals living near hazardous waste sites. Such studies are especially necessary because the majority of animal studies currently available utilize rats, which are not a relevant model for humans for reproductive effects involving disruption of hormonal control of cyclicity and reproductive senescence. Several studies are available that used pigs, with similar results to the rat studies (disruption of estrus cyclicity and/or anestrus); the relevance of pigs as a model for humans for atrazine's effects on hormonal control has not been determined. Studies examining the mechanism of action of atrazine in pigs on estrus cyclicity would be helpful in determining the relevance of pigs as a reproductive model for humans.

Biomarkers of Exposure and Effect.

Exposure. Atrazine is primarily excreted in the urine as dealkylated metabolites and mercapturic acid derivatives (Bakke et al. 1972; Buchholz et al. 1999; Catenacci et al. 1993; Gojmerac and Kniewald 1989; Meli et al. 1992; Timchalk et al. 1990), which can be detected in urine at levels as low as 1 μg/L (Ikonen et al. 1988). Atrazine and its metabolites can also be detected in blood and tissues at levels as low as 14.25 ng/g (Pommery et al. 1993). The detection of atrazine in urine or tissues may be a specific biomarker for atrazine exposure, but <2% of atrazine is excreted in the urine unchanged (Buchholz et al. 1999; Catenacci et al. 1993). The detection of atrazine metabolites is not necessarily specific for atrazine exposure, but may indicate exposure to other triazine herbicides such as cyprazine, simazine, or propazine (Bradway and Moseman 1982; Hanioka et al. 1999; Larsen and Bakke 1975). There is no quantitative relationship between exposure levels and levels of atrazine or metabolites found in the body or in urine (Lucas et al. 1993). Additional studies are needed to establish a relationship between exposure level and urinary concentration of atrazine metabolites.

Effect. The primary target organs of atrazine are the female reproductive system and the liver. The reproductive effects in animals included altered estrus cyclicity or anestrus (Cooper et al. 1996b, 2000; Ćurić et al. 1999; Eldridge et al. 1994a, 1999a; Gojmerac et al. 1996, 1999; Šimić et al. 1994; Wetzel et al. 1994), altered serum and/or pituitary hormone levels (Cooper et al. 1996b; Eldridge et al. 1994a; Gojmerac et al. 1996, 1999), reduced fecundity (Šimić et al. 1994),), increased litter resorption (Narotsky et al. 2001), decreased ovarian and uterine weights (Ashby et al. 2002; Eldridge et al. 1994a), and ovarian

histopathology (Ćurić et al. 1999; Gojmerac et al. 1996). The hepatic effects seen following atrazine exposure were increased serum lipids and liver enzymes (Gojmerac et al. 1995; Morichetti et al. 1992; Radovcic et al. 1978; Santa Maria et al. 1987; Wurth et al. 1982), liver histopathology (Ćurić et al. 1999; Gojmerac et al. 1995), changes in liver weight (Aso et al. 2000; EPA 1984f, 1987d, 1987f), and changes in trigycerides and globulin levels (EPA 1984f, 1987d). While all of these effects may be useful biomarkers to indicate possible atrazine exposure, none are specific for atrazine. Additionally, it is unclear which, if any, of the above reproductive effects may occur in humans following atrazine exposure. Development of additional, more sensitive biomarkers that are specific for atrazine effects would be useful in monitoring populations at high risk. This may need to be done in tandem with the determination of the interaction of atrazine, if any, with the hypothalamus in humans and the elucidation of the mechanism of that interaction.

Absorption, Distribution, Metabolism, and Excretion. The absorption, distribution, metabolism, and excretion of atrazine has been investigated in humans and animals. The only available inhalation toxicity studies in humans involved occupational exposure to very large atrazine particles (30–70 μm) (Catenacci et al. 1990, 1993), which made it unlikely that any significant amount of atrazine reached the lungs. Evidence of absorption following oral exposure was provided by a single case report of a man who ingested a weedkiller containing atrazine and other chemicals; atrazine was detected in the plasma and several organs at autopsy (Pommery et al. 1993). Absorption of atrazine following dermal exposure has been evidenced by the presence of atrazine and its metabolites in urine of people exposed to radiolabelled Aatrex (a commercial product containing atrazine) via a forearm patch (Buchholz et al. 1999), and in urine of workers exposed primarily via dermal contact (Catenacci et al. 1990, 1993). An *in vitro* study using human skin samples also indicated that limited absorption (16.4% in 24 hours) occurs through the skin (Ademola et al. 1993). Further evidence of absorption following oral (Meli et al. 1992; Timchalk et al. 1990) and dermal (Hall et al. 1988) exposure to atrazine has been provided by animal studies showing the presence of atrazine and its metabolites in the plasma, urine, and/or feces. Absorption following gavage administration has been described as a first-order process with an absorption half-life of 2.6 hours (Timchalk et al. 1990), with 37–57% of the administered dose recovered in the urine and 14% in the feces (Meli et al. 1992; Timchalk et al. 1990). Animal studies to determine the absorption efficiency of inhaled atrazine would be useful for determining the risk to occupationally exposed individuals.

Data on distribution of atrazine in humans after oral exposure was limited to a single case report of a 38-year-old man who died of progressive organ failure and shock 3 days after ingesting 500 mL of a

weedkiller that contained 100 g atrazine, 25 g of aminotriazole, 25 g of ethylene glycol, and 0.15 g of formaldehyde (Pommery et al. 1993). At autopsy, atrazine was detected in the kidney, small intestine, lung, liver, pancreas, muscle, heart, and plasma. Radioactivity was detected in the plasma, whole skin, and carcass of rats gavaged with 30 mg/kg [C^{14}]-atrazine (Timchalk et al. 1990), and in the liver, brain, heart, lung, kidney, digestive tract, omental fat, and skeletal muscle of rats gavaged with up to 17.7 mg/kg [C^{14}]-atrazine (Bakke et al. 1972). Animal studies to determine the distribution following inhalation and dermal exposure to atrazine would be useful for evaluating the exposure and risk of occupationally exposed individuals.

Atrazine is extensively and rapidly metabolized as indicated by plasma levels of atrazine and the relative amounts of metabolites and parent compound in the urine within 8–24 hours after exposure. Plasma levels of ^{14}C from radiolabeled atrazine have been shown to peak at 8–10 hours postexposure in rats, and the rate of clearance half-life has been calculated to be 10.8–11.2 hours (Timchalk et al. 1990). In urine, unchanged atrazine has been detected, but comprised <2% of all atrazine-related compounds after dermal exposure in humans (Buchholz et al. 1999; Catenacci et al. 1993) or oral exposure in rats (Meli et al. 1992). In humans, 50% of all urinary atrazine metabolites were excreted within 8 hours and 100% within 24 hours (Catenacci et al. 1993). In rats, approximately 57% of the radioactivity from administered [^{14}C]-atrazine was excreted in the urine within 24 hours (Timchalk et al. 1990), and urinary atrazine metabolites decreased to 1/30 or less of the 24-hour level by 48 hours postexposure (Meli et al. 1992).

Atrazine is primarily metabolized in humans via dealkylation, probably followed by glutathione conjugation and conversion to mercapturic acids. This is apparently true regardless of route of exposure (Buchholz et a. 1999; Catenacci et al. 1993; Meli et al. 1992; Timchalk et al. 1990). *In vitro* studies using microsomal preparations from liver and other tissues of humans and animals have indicated that dealkylation of atrazine is mediated by cytochrome P-450 enzymes (CYPs) (Adams et al. 1990; Ademola et al. 1993; Croce et al. 1996; Hanioka et al. 1998a, 1999; Lang et al. 1996, 1997; Meli et al. 1992; Venkatesh et al. 1992). In humans, the primary CYP responsible for phase I metabolism is probably CYP1A2 (Lang et al. 1997), and in rats, CYPs 2B1 and 2C11 have been implicated as the primary metabolic enzymes (Hanioka et al. 1998a). Available data indicate that phase II metabolism of atrazine proceeds through glutathione conjugation and mercapturic acid formation (Adams et al. 1990; Egaas et al. 1995). Additional studies examining the enzymes responsible for phase I and phase II metabolism and the ratio of products would be useful.

Specific data on elimination and excretion of atrazine by any route were limited. However, the primary route of excretion appears to be in urine, as indicated by the detection of urinary atrazine and its metabolites in a number of species exposed via oral and dermal routes (Bakke et al. 1972; Buchholz et al. 1999; Catenacci et al. 1990, 1993; Meli et al. 1992; Timchalk et al. 1990). Fecal excretion was a minor route (Buchholz et al. 1999; Timchalk et al. 1990). No data were located regarding enterohepatic circulation and biliary secretion or excretion of atrazine in breast milk. Studies to determine whether enterohepatic circulation occurs and the extent to which it occurs, and studies examining the release of atrazine and its metabolites in breast milk would be helpful in better defining exposure.

Comparative Toxicokinetics. Available data indicate that atrazine is readily absorbed through the intestinal tract (Meli et al. 1992; Pommery et al. 1993; Timchalk et al. 1990) and that limited absorption occurs through the skin (Ademola et al. 1993; Buchholz et al. 1999; Catenacci et al. 1990, 1993; Hall et al. 1988) in humans and animals. Studies examining absorption following inhalation exposure in humans (occupational exposure) and animals would be useful.

Atrazine was detected in the kidney, small intestine, lung, liver, pancreas, muscle, heart, and plasma of a man who ingested weedkiller containing atrazine (Pommery et al. 1993). Radioactivity was detected in the liver, brain, heart, lung, kidney, digestive tract, omental fat, and skeletal muscle of rats gavaged with [C^{14}]-atrazine (Bakke et al. 1972). Additional studies to determine the relative distribution of atrazine and its metabolites in internal organs after inhalation, oral, and dermal exposure to atrazine would be useful. Studies to determine if atrazine crosses the placenta in pregnant animals would also be useful.

While atrazine metabolites have been shown to be qualitatively similar across species, quantitative differences and differences in rate of formation and ratio of products have been observed (Adams et al. 1990; Hanioka et al. 1999; Lang et al. 1996). Inter- and intra-species and age and sex differences in glutathione S-transferase (GST) activity have also been seen (Egaas et al. 1995). Additional studies examining potential sex- and age-related differences between and within species would be useful.

Only 0.3–4.4% of an applied dose of [C^{14}]-atrazine was recovered in urine and 0.0–0.7% in feces of people exposed dermally via an arm patch (Buchholz et al. 1999). No studies were located regarding excretion in humans after oral exposure to atrazine. In rats exposed orally to [C^{14}]-atrazine, 57% of the administered radioactivity was excreted in the urine and only 14% in the feces (Timchalk et al. 1990). Additional studies on routes of elimination of atrazine following exposures of animals by the inhalation, oral, and dermal routes would be useful.

Methods for Reducing Toxic Effects. Oral absorption of atrazine can be reduced with gastric lavage, activated charcoal, sodium sulfate, and cathartics (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990); however, animal studies indicate that gastrointestinal absorption of atrazine is fairly rapid (absorption half-life of 2.6 hours) (Timchalk et al. 1990) and thus, these measures would need to be employed soon after exposure. Dermal absorption of atrazine can be reduced by removing contaminated clothing and thoroughly washing the exposed skin with a mild soap (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990). Additional data regarding interference with gastrointestinal absorption would be useful.

Since animal studies indicate that atrazine is rapidly metabolized and cleared from the body, methods for reducing body burden are not expected to be especially effective in reducing human exposures.

The primary effect of atrazine in rats is disruption of estrus cyclicity, which is mediated through an alteration of the gonadal-hypothalamic-pituitary axis. Differences in reproductive physiology between rats and humans make it unlikely that this mechanism would occur in humans. However, similar effects are seen in pigs and the mechanism has not been elucidated. Additionally, it is not known whether atrazine or its metabolites are responsible for these effects. Studies in pigs and other animals (except rats) to elucidate the mechanism for the reproductive effects of atrazine may be useful for developing methods that can interfere with these effects.

Children's Susceptibility. A single cohort study of farm couples in Canada indicated that atrazine exposure may be associated with increased preterm delivery and miscarriage (Arbuckle et al. 2001; Savitz et al. 1997), and an ecological study indicated that atrazine levels in drinking water were positively associated with decreased intrauterine growth rates and increased birth defects in the respective communities (Munger et al. 1992b, 1997). Additional epidemiological studies examining these associations may be useful.

Developmental effects have been observed following pregestational, gestational, and lactational exposure of rat dams to atrazine. The observed effects included postimplantation losses (Infurna et al. 1988), decreases in fetal body weight (Infurna et al. 1988), incomplete ossification (Infurna et al. 1988), neurodevelopmental effects (Peruzović et al. 1995), and impaired development of the reproductive system (Stoker et al. 1999). A neurodevelopmental toxicity study is needed to verify and further characterize the Peruzović et al. (1995) results.

There are no studies that indicate that metabolism of atrazine differs between children and adults. The primary pathway by which atrazine is metabolized is dealkylation to yield the mono- and/or didealkylated atrazine derivatives. A study by Lang et al. (1997) indicated that CYP1A2, CYP2C19, and CYP1A1 may be the major CYP enzymes for atrazine, but that other forms, including CYP2A6, CYP2C9, and CYP2B6, are likely to be major contributors, especially in individuals with low levels of CYP2C19 or CYP1A2. While CYP2C19 and CYP1A2 are not present in appreciable levels in human fetal liver, their activities increase to adult levels by 4–6 months of age (Leeder and Kearns 1997; Ratenasavanh et al. 1991; Sonnier and Cresteil 1998). GST activity, involved in phase II metabolism of atrazine, generally reaches adult levels by 6–18 months of age (Leeder and Kearns 1997). Studies examining the metabolic differences between children and adults may be useful. Studies to determine if atrazine or its metabolites cross the placenta of animals and enter the developing fetus and if they are present in breast milk would also be very useful.

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 of atrazine are outlined in Table 3-4 (CRIS 2002; FEDRIP 2002).

The group, triazines and their degradation products, is listed on the EPA's Contaminant Candidate List (CCL) (EPA 2002b). The CCL is a published list of contaminants that are known or are anticipated to occur in public drinking water systems and may require regulation under the Safe Drinking Water Act (SDWA). The CCL contains priority contaminants for EPA's drinking water program activities, including drinking water research, monitoring, guidance development, and regulation determination. A specific area of research for triazines and their degradation products is focused on their mechanism of carcinogenicity (EPA 2002b).

Table 3-4. Ongoing Studies on the Health Effects of Atrazine[a]

Investigator	Affiliation	Research description
Filipov NM	CSREES, USDA	Assessment of dopaminergic neurotoxicity of several agricultural pesticides in adolescent, adult, and aged mice
Lasley BL	University of California; Davis, California	Methods development for quantification of estrogen receptor- and aryl hydrocarbon receptor-binding xenobiotics that may cause adverse effects on human reproductive health
Lemley AT; Snedeker SM	CSREES, USDA	Determination of the adverse effects to human and environmental health of agrochemicals detected in homes of pesticide applicators and farmers in rural central New York
Perry MJ	School of Public Health, Harvard University; Boston, Massachusetts	The effects of atrazine on reproductive hormone production (including follicle stimulating hormone, luteinizing hormone, and testosterone) among pesticide applicators
Rayburn AL	CSREES, USDA	Low level agrichemical exposure and chromosomal aberrations in tree frog tadpole cells
Tchounwou PB	Jackson State University, Jackson Mississippi	Toxicokinetics, histopathology, and *in vivo* genotoxicity in rats and fish

[a]Source: CRIS 2002; FEDRIP 2002

CSREES = Cooperative State Research, Education, and Extension Service; USDA = U.S. Department of Agriculture

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

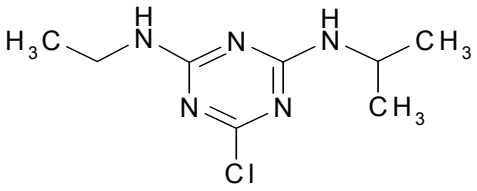
Information regarding the chemical identity of atrazine is located in Table 4-1.

Atrazine is produced commercially in the United States as a technical-grade chemical with a purity of 92–97% (IARC 1999) to 99.9% (EPA 1983) active ingredient. Impurities in the former formulation included dichlorotriazines, hydroxytriazines, and tris(alkyl)aminotriazines.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of atrazine is located in Table 4-2.

Table 4-1. Chemical Identity of Atrazine

Characteristic	Information	Reference
Chemical name:	Atrazine	EPA 1983; Howard 1991
Synonyms:	6-Chloro-n-ethyl-n'-(1-methylethyl)-triazine-2,4-diamine; 2-Chloro-4-ethylamino-6-iso-propylamine-s-triazine; 2-Chloro-4-(ethyl-amino)-6-(isopropylamino)-s-triazine; 2-Chloro-4-(ethylamino)-6-(isopropylamino)-triazine; Chloro-4-(propylamino)-6-ethyl-amino-s-triazine; Chloro-3-ethylamino-5-iso-propylamino-2,4,6-triazine; Butyl-n-(acetyl)-aminopropionic acid	
Registered trade names:	Aatrex®, Aatram®, Atratol®, Gesaprim®	EPA 1983; Syngenta 2000
Chemical structure:		
Identification numbers:		
CAS registry	1912-24-9	HSDB 2002
NIOSH RTECS	XY5600000	HSDB 2002
DOT/UN/NA/IMO	UN 2763	HSDB 2002
	UN 2997	HSDB 2002
	UN 2764	HSDB 2002
	UN 2998	HSDB 2002
	IMO 6.1	HSDB 2002
	IMO 3.2	HSDB 2002
HSDB	413	HSDB 2002
Experimental code number	G-30027 (Ciba-Geigy)	Farm Chem Handbook 2001

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; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Atrazine

Property	Information	Reference
Molecular weight	215.69	HSDB 2002
Color	White colorless	HSDB 2002
Physical state	Colorless powder Colorless crystals	IARC 1999 Verschueren 2001
Melting point	173–175 °C	HSDB 2002
Density	1.23 g/cm^3 (22 °C)	HSDB 2002
Odor	Odorless	NIOSH 1994
Solubility:		
at 22 °C	Soluble in water (34.7 mg/L)	Ward and Weber 1968
at 25 °C	Soluble in ethylacetate (24 g/L), acetone (31 g/L), dichloro-methane (28 g/L), ethanol (15 g/L), toluene (4 g/L), n-hexane (0.11 g/L), and n-octanol (8.7 g/L)	Tomlin 1997
at 27 °C	Soluble in n-pentane (360 mg/L), diethyl ether (12,000 mg/L), methanol (18,000 mg/L), ethyl acetate (28,000 mg/L), chloroform (52,000 mg/L), and dimethyl sulfoxide (183,000 mg/L)	Humburg 1989
Partition coefficients:		
Log K_{ow}	2.60 2.71	Hansch et al. 1995 Brown and Flagg 1981
Log K_{oc}	1.96 1.97 2.98 3.38 2.18 2.53 2.33	Dousset et al. 1994 Green et al. 1993 Koskinen and Rochette 1996 Koskinen and Rochette 1996 Meakins et al. 1995 Meakins et al. 1995 Weber 1991
Vapor pressure at 25 °C	2.89x10^{-7} mmHg	Tomlin 1997
Henry's Law constant at 25 °C	2.96x10^{-9} atm-m^3/mol	Riederer 1990
pK_a	1.68	Bailey et al. 1968
Hydrolysis rate constant at 25 °C	2.735x10^{-11} cm^3/molecule-second (estimated)	Meylan and Howard 1993
Autoignition temperature	No data	
Flashpoint	Not applicable	EPA 1983
Flammability limits	Not applicable	EPA 1983

Table 4-2. Physical and Chemical Properties of Atrazine

Property	Information	Reference
Conversion factors[a]	mg/m^3=8.82xppm	HSDB 2002; IARC 1999
Explosive limits	Not applicable	EPA 1983

[a]In air, atrazine is both present in the gas phase and associated with particulates (HSDB 2002). Conversion factors are only applicable for those compounds that exist entirely in the vapor phase. Therefore, while this conversion factor has been reported in the literature, its use is not recommended, as it will not provide an accurate reflection of ambient air atrazine concentrations.

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

5.1 PRODUCTION

Atrazine is produced by a continuous process where isopropylamine is reacted with cyanuric acid under basic conditions, forming 2,4-dichloro-6-isopropylamino-s-triazine, which is then reacted with monoethylamine and dilute caustic to form atrazine. The approach allows for continuous product recovery, solvent recycling, and waste removal (IARC 1999; UDC 1977). The triazine herbicides were first synthesized in 1955 (Kroschwitz and Howe-Grant 1995) and atrazine was first registered for use by the Ciba-Geigy Corporation in 1958 (Ribaudo and Bouzaher 1994). It has been used over the last 40 years as an effective broad-leaf herbicide in corn, sorghum, and sugar cane, and has also been used for other crops and for nonspecific treatment of weeds along railway right of ways and highways. Some of the latter uses have been curtailed to lessen atrazine release into surface waters.

Atrazine is designated as a restricted use pesticide (RUP), and is not available to the general public. RUPs are, by law, for retail sale to, and for use by, only certified applicators or persons under their direct supervision, and only for those purposes covered by the applicator's certification. Atrazine received this classification on January 23, 1990 (Fishel 2000). Current trade names for atrazine include Aatrex®, Atranex, Atred, Gesaprim®, Primatol, and Vectal (Trochimowicz et al. 2001). Atrazine is available in different formulations, including suspension concentrates, wettable powders, flowable liquids, and water-dispersible granules (HSDB 2002).

There are 24 facilities that manufacture or process atrazine (Table 5-1). The amounts manufactured or processed range from 1,000 to 9,999 pounds in Georgia to very large formulation activities (1,000,000–9,999,999 pounds) in Alabama, Mississippi, and Missouri. Facilities in Arkansas and Iowa also process atrazine in large amounts (up to 9,999,999 pounds), but Louisiana houses facilities that process the greatest amounts of atrazine (up to 49,999,999 pounds), with activities including production, processing, manufacturing, reaction, sale and distribution, and other ancillary uses.

Table 5-2 shows the six companies that are registered to produce products containing atrazine. Most of these companies produce a technical-grade atrazine, with a purity ranging from 95.2 to 97%, although higher purity atrazine can be produced (>99%) (EPA 1983). The technical-grade compound may contain

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	1	1,000,000	9,999,999	6
AR	2	10,000	9,999,999	2, 3, 7, 12
FL	4	10,000	999,999	7, 8, 12
GA	1	1,000	9,999	7
IA	3	100,000	9,999,999	1, 3, 7, 9
IL	2	10,000	999,999	7, 12
LA	1	10,000,000	49,999,999	1, 3, 4, 7, 9, 12, 13, 14
MI	1	100,000	999,999	7
MO	2	1,000,000	999,999,999	2, 4, 7, 9
MS	1	1,000,000	9,999,999	2, 3, 4, 7, 9
NE	3	1,000	9,999,999	1, 4, 7, 9, 12
OH	3	100	999,999	7, 12

Source: TRI01 2003

[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

Table 5-2. Registered Atrazine Manufacturing-use Products[a]

Formulation	EPA registration number	Registrant
97% T	100-529	Novartis Crop Protection, Inc. (formerly Ciba-Geigy Corp.)
97% T	19713-7	Drexel Chemical Company
92.15% T[b]	19713-375	Drexel Chemical Company
97% T[b]	34704-784	Platte Chemical Company, Inc.
97% T	35915-63[c]	Oxon Italia S.P.A.
97.2% T	11603-32	Agan Chem Mfg. Ltd.
95.2% T	67604-1	Sanachem (PTY) Ltd.

[a]Adapted from EPA 2001a
[b]Repackaged from an EPA-registered product.
[c]Transferred May 23, 1988 from Ida, Inc. (EPA Reg No. 54115-63), which was transferred October 13, 1987 from Axon Corporation.

T = technical

three classes of impurities, namely dichlorotriazines, hydroxytriazines, and tris(alkyl)aminotriazines. These impurities have not been quantified in the available literature.

5.2 IMPORT/EXPORT

Data on import and export of atrazine are limited. The most recent import and export data available are for the year 1972 (HSDB 2002); a negligible amount was imported, and exports were reported as 9.08×10^6 kg (19,000,000 pounds). Bason and Colborn (1998) did not provide any 1990 export information for atrazine.

5.3 USE

Atrazine is the most heavily used pre- and postemergence herbicide in the United States (Trochimowicz et al. 2001). It is used for the control of grasses and broad-leafed weeds, and is primarily used on corn, sorghum, sugarcane, macadamia nuts, and conifer tree crops; over 65% of the corn crop acreage in the United States is treated with atrazine (USDA 1993). Atrazine has been used in this capacity as a broad leaf herbicide for the last 35 years (IARC 1999). It should be used at the appropriate application rates, which have been reduced to 1.4–2.0 pounds per acre (Johnson et al. 1996). The EPA has estimated that 31–35 million kg of active ingredient atrazine were used on agricultural crops in the years 1987, 1993, and 1995 (IARC 1999).

More specific information is available from a National Center for Food and Agricultural Policy document that reported trends in pesticide use between 1992 and 1997 (NCFAP 2000). Atrazine use showed a slight (3%) increase in use from 1992 to 1997. In 1992, 73,315,295 pounds (33 million kg) were used, and in 1997, 74,560,407 pounds (34 million kg) were used (NCFAP 2000). Corn and sugarcane crops received significant increases in atrazine treatment in 1997 as compared to 1992; sugarcane crops received 503,000 more pounds and corn crops received 2,037,000 more pounds. Sorghum crops, in contrast, were treated with 1,065,000 pounds less in 1997 as compared to 1992. This, however, was likely related to much less sorghum being planted in 1997 as compared to 1992 (NCFAP 2000). It should be noted, however, that in some areas, corn growers decided to replace atrazine pre- and posttreatments with other products. This decision was a result of restrictions placed on the use of atrazine, such that the application rate restrictions reduced effectiveness on certain weeds (NCFAP 2000).

There are seven EPA registered manufacturing-use products, as shown in Table 5-2.

Atrazine usage rates have been relatively constant since monitoring began, but are beginning to decrease. In 1993, 4,955,300 pounds (2,247,093 kg) of atrazine were used on 45,333,000 acres (18,346,014 hectares) of corn in the United States (Ribaudo and Bouzaher 1994); the maximum reported usage was in 1976, when 9,034,000 pounds (4,097,796 kg) of atrazine were used in all agricultural applications. Of that, 8,379,000 pounds (3,800,689 kg) were applied to corn. Also in 1976, the largest number of acres was treated with atrazine, with 61,750,000 total acres (24,989,883 hectares) being treated. More than 92% of the total acreage treated with atrazine (56,863,000 acres; 23,012,141 hectares) were corn crops (Ribaudo and Bouzaher 1994). Atrazine is a restricted use pesticide and is only available to applicators who meet appropriate requirements of the state and federal government.

5.4 DISPOSAL

Atrazine and waste containing atrazine are considered toxicity class III—slightly toxic by the EPA (Extoxnet 1996). It does not require any special hazardous waste disposal procedures, according to EPA Resource Conservation and Recovery Act listings, either by specific listing or due to reactivity, ignitability, corrosivity, or toxicity, as it is not considered a hazardous waste. However, atrazine is included in the Priority Group 1 of pesticide tolerances that will be examined first under the Food Quality Protection Act (FQPA) tolerance reassessment (62 FR 42020) (FEDRIP 1998).

Disposal may be achieved by different means. Atrazine is completely degraded by wet oxidation (HSDB 2002), and 99% of atrazine is decomposed when burned in a polyethylene bag. Increasing combustion temperatures by use of a hydrocarbon fuel would appear to be suitable for small quantities of waste, but larger quantities would require the use of a caustic wet scrubber to remove nitrogen oxides and hydrochloric acid from the resulting combustion gases. The recommended method of atrazine disposal is to react atrazine wettable powders with sufficient 10% (weight/volume) aqueous sodium hydroxide to ensure a pH of >14. The solution may be heated to increase the rate of hydrolysis. When completely hydrolysed, the resulting solution should be diluted with excess water and washed into the sewer (HSDB 2002).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Atrazine has been identified in at least 20 of the 1,636 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2003). However, the number of sites evaluated for atrazine is not known. The frequency for these sites within the United States can be seen in Figure 6-1. Of these sites, all 20 are located within the United States and none are located in the Commonwealth of Puerto Rico (not shown). Significant amounts of atrazine are also released during manufacture, formulation, transport, storage, and disposal (see Section 6.2 below).

Atrazine is an extensively-used, broad leaf herbicide, and virtually the entire production volume is released to the environment as a result of agricultural and other weed-control practices. In its recommended applications, atrazine is used as a preemergence and postemergence herbicide for corn, sorghum, sugarcane, macadamia nuts, and other crops, as well as in conifer reforestation, and as a nonspecific herbicide for the treatment of fallow soil and highway right-of-ways. Therefore, most environmental atrazine releases will occur as a result of its intended usage. There are no known natural sources of atrazine.

While atrazine is a widely-used herbicide, it is not available to the general public, as it is classified as a restricted-use pesticide (RUP). RUPs are, by law, only for retail sale to and use by certified applicators or persons under their direct supervision, and only for those purposes covered by the applicator's certification. Atrazine received this classification on January 23, 1990 (Fishel 2000).

The normal agricultural use of atrazine will result in some loss or transport from the soil into the atmosphere, where it may later undergo deposition back to soils or into bodies of water. Some atmospheric release of atrazine will also occur as a result of its formulation, manufacture, and disposal. It may also enter air by loss of applied herbicide before it reaches the soil, and by particle distribution of dusts that contain atrazine. Volatilization of atrazine following application to fields has been measured to be up to 14% of the applied amount. Once in the air, atrazine will exist in both the particulate and vapor phases due to its vapor pressure. These forms will influence how atrazine is transported or later deposited on to terrestrial or aquatic environments.

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

Atrazine's concentration in air will vary with application season; measured concentrations have ranged from just above the detection limit (~0.03 ng/m^3) to more typical concentrations of 0.20–0.32 µg/m^3. As a result of atrazine's vapor and particulate phase distribution, and climate patterns during and following application, it can be transported in the atmosphere significant distances from its application area; it has been detected as far as 100–300 km (62–186 miles) from the closest application area. While in the atmosphere, it has not been observed to undergo direct photolytic degradation. However, vapor-phase atrazine can be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals. Particulate-phase atrazine will be removed from the atmosphere by wet and dry deposition; atrazine is commonly found in rainwater in the seasons following agricultural applications.

Atrazine may also be transported from where it is applied to soils by runoff into surface water and percolation into groundwater. Atrazine tends to persist in surface and groundwater, with a moderate tendency to bind to sediments. Slow or no biodegradation occurs in surface water or groundwater environments, respectively. When it is degraded in aquatic systems, hydroxyatrazine, deethylatrazine, and deisopropylatrazine are the major products formed by chemical and biological processes. Depending on the availability of sunlight, oxygen, microorganisms, and plants, the half-life of atrazine in water tends to be longer than 6 months; in some cases, no degradation of atrazine has been observed in aquatic systems. This lack of degradability is one reason that atrazine is commonly observed in surface waters and well-water drinking water supplies. This long residence time in surface waters indicates that it may have the opportunity to enter the food chain. Atrazine has a slight to moderate tendency to bioconcentrate in microorganisms, algae, aquatic invertebrates, worms, snails, or fish. It is only slightly toxic or nontoxic to fish and other aquatic invertebrates, and has been shown to have short-term effects on fish behavior.

Atrazine is not very persistent to moderately persistent in surface soils, with reported half-lives commonly ranging from 14 to 109 days. However, it has been observed to persist in some soils for up to 4 years, and there are instances where no biodegradation has been observed in some subsurface soils or in aquifer materials. It can be detected in soils where it has been applied as a pesticide, as well as in soils that have been impacted by runoff or by atmospheric deposition. In soils, it may undergo abiotic hydrolysis to hydroxyatrazine, but this occurs very slowly unless dissolved organic matter is present or the soils are extremely acidic. It is generally biodegraded by soil microorganisms to hydroxyatrazine, deethylatrazine, or deisopropylatrazine, with subsequent metabolism to cyanuric acid. This may be followed by relatively complete degradation to CO_2 (mineralization) within 20 weeks. Anaerobic biodegradation occurs very

slowly, with half-lives of over 200 days. This half-life may include some abiotic degradation since hydroxyatrazine was the only observed degradation product. Atrazine, however, has been reported to degrade more quickly in anaerobic soil under strongly reducing conditions.

Even though atrazine is a widely used pesticide for corn, sugarcane, macadamia nuts, sorghum, and other crops, very few atrazine residues have been found in food analyses conducted by the FDA and the USDA from 1987 to the present. Atrazine concentration was very low (0.001–0.028 μg/g) in the few samples where it was detected. In contrast, atrazine has been detected in many drinking water well samples, especially in the areas where it is used on corn crops. These data suggest that most members of the general population have little or no exposure to atrazine from foods. People who use products that contain atrazine, however, such as those involved in farming, or during its manufacture, or in other uses where atrazine has been approved, are more likely to be exposed to atrazine. It has been estimated that approximately 1,000 industrial workers are exposed to atrazine per year (NIOSH 1989). People who live in regions where atrazine is used may be exposed to atrazine in drinking water that is obtained from wells. In studies of drinking water wells in midwestern states, atrazine was found in up to 41% of the municipal wells tested (Kolpin et al. 1997a). In Maine, it was detected in 31% of the drinking water wells (Bushway et al. 1992). Nationwide, the EPA estimated that atrazine was present in 1,570 community water source (CWS) wells and in 70,800 rural domestic wells (EPA 1990a).

6.2 RELEASES TO THE ENVIRONMENT

All atrazine is commercially produced for the control of broad-leaf and other weeds, in formulations designed for preemergence or postemergence of crops, or for weed control in nonspecific applications, such as the treatment of fallow land or highway right-of-ways. Therefore, all manufactured atrazine is expected to be released to the environment, primarily soils, during these activities. Release data generated for the Toxics Release Inventory (TRI) (e.g., Table 6-1) also details release, 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 atrazine, since it is one of the most widely-used agricultural herbicides in the United States, the TRI data represent only a small fraction of the environmental release.

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Atrazine

Reported amounts released in pounds per year[a]								
State[b]	Number of facilities	Air[c]	Water	Under-ground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
AL	1	672	11	0	0	683	0	683
AR	2	500	5	0	0	505	250	755
FL	4	250	No data	0	510,160	510,410	187,372	697,782
GA	1	0	No data	0	0	0	0	0
IA	3	3,428	0	0	0	3,428	12,933	16,361
IL	2	521	No data	0	0	521	500	1,021
LA	1	18,816	668	535	0	20,019	13,628	33,647
MI	1	10	0	0	0	10	0	10
MO	2	158	0	0	0	158	0	158
MS	1	500	250	0	0	750	0	750
NE	4	7	0	0	0	7	38	45
OH	2	10	0	0	0	10	755	765
Total	24	24,872	934	535	510,160	536,501	215,476	751,977

Source: TRI01 2003

[a]Data in TRI are maximum amounts released by each facility.
[b]Post office state abbreviations are used.
[c]The sum of fugitive and stack releases are included in releases to air by a given facility.
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[e]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

Table 6-1 shows the 2001 TRI releases of atrazine from manufacturing or processing facilities to different environmental compartments. Most of the atrazine released to the environment from these facilities was released to soils. Of the 24 facilities producing or processing atrazine, 15 facilities reported that a total of 24,872 pounds (11,282 kg) were released to the air, four facilities reported releasing 934 pounds (423 kg) to surface water, one facility reported release of 535 pounds (243 kg) by underground injection, and three facilities reported release of 510,160 pounds (231,405 kg) to land (TRI01 2003). The releases to land represented 95% of the total releases of atrazine (TRI01 2003). All three sites reporting releases to land are located in Florida. Two of those sites were owned by one company, and the combined amount released to land from those two sites was over half (51%; 260,160 pounds; 118,007 kg) of the total atrazine released to land. These high releases in Florida were a result of Standard Industrial Code activities related to sugar cane and sugar beet processing, and activities related to disposal and refuse systems (# 4953).

Release of atrazine from these facilities has changed from year to year since the TRI listing for atrazine began in 1995 (TRI01 2003). Reported air releases have ranged from a low of 20,946 pounds (9,501 kg) released in 1999 to a high of 35,119 pounds (15,930 kg) released in 1997. Surface water releases have ranged from a low of 934 pounds (423 kg) released in 2001 to a high of 2,756 pounds (1,250 kg) released in 1998. Land releases have fluctuated more, with the lowest amount (388,928 pounds; 176,417 kg) being released in 1997 and the highest amount (637,036 pounds; 288,958 kg) being released in the year that reporting began (1995). It should be emphasized, however, that TRI does not report agriculture-related releases, and that atrazine is one of the most widely used herbicides in the United States. For example, in 1981, for the state of New York alone, an estimated 2,495,800 pounds (1,132,087 kg) of atrazine were applied to soils for herbicidal use (Walker and Porter 1990).

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 weed treatment usage, atrazine has been identified in several environmental compartments including surface water, groundwater, soil and sediment collected at 20 of the 1,636 current or former NPL hazardous waste sites (HazDat 2003).

6.2.1 Air

Atrazine has been detected in the atmosphere, both nearby and distant from areas where it has been applied as a pesticide. In addition to detecting atrazine in the atmosphere in the vicinity of and distant from where it is used in agricultural or other broad-leaf weed control activities, atrazine has also been detected in the air near 14 of 22 manufacturing or processing facilities that report atrazine releases (TRI01 2003). The total amount of atrazine released to the atmosphere by these sites was 33,807 pounds (15,335 kg). In contrast to detecting atrazine in the atmosphere in relation to TRI-reported manufacture, processing, or agricultural practices, atrazine was not identified in air samples near the 20 sites collected from the 1,636 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2003).

When atrazine was measured in the air near its agricultural or other applications, in some cases, it was only been found in the atmosphere during the first month following the application of the herbicide to crops (Elling et al. 1987). In other cases, it was found at 4 months (Chevreuil et al. 1996) to 8 months afterwards (Wu 1981). The manner in which atrazine is applied to the fields may influence its entry (i.e., volatilization) to the atmosphere. Cumulative volatilization of atrazine from conventionally- tilled fields was equal to 14% of the amount applied, but only 9% of the total applied amount was volatilized from no-till fields (Weinhold and Gish 1994). Glotfelty et al. (1989) measured the volatilization of atrazine and other pesticides from moist and dry soils, and found that 2.4% of the applied atrazine had volatilized after 21 days. The total mass of atrazine that was volatilized to the atmosphere can be calculated using these percentages and the quantities used on croplands. The highest reported amount of atrazine used on croplands was 90,340,000 pounds in 1976 in the United States (Section 5.3; Ribaudo and Bouzaher 1994). If one assumes that 2.4% of this volatilized, then the amount of atrazine was distributed to the atmosphere was 2,168,160 pounds. If one assumes that 14% was volatilized, then 12,647,600 pounds was distributed to the atmosphere. The lowest amount of atrazine reported was in 1964, where 10,837,000 pounds of atrazine was used on all crops (Ribaudo and Bouzaher 1994). In this case, 2.4% volatilization would represent 260,088 pounds being distributed to the atmosphere; 14% volatilization would represent 1,517,180 pounds being distributed. For comparison, in 1997, 74,560,407 pounds of atrazine was applied to crops in the United States (NCFAP 2000). If one assumes that 2.4% of this volatilized, then this represents 1,789,450 pounds of atrazine being distributed to the atmosphere. If one assumes that 14% was volatilized, then this represents 10,438,457 pounds. In all cases, the amounts distributed to the atmosphere represent significantly more than the amounts distributed to the atmosphere as a result of manufacture or disposal.

6.2.2 Water

According to the TRI, 1,034 pounds (469 kg) of atrazine were released to water from four facilities that manufacture or process atrazine (TRI01 2003). Atrazine has been identified in groundwater and surface water at 12 and 9 of the 1,636 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 2003). Atrazine may also be found in surface and groundwater as a result of its formulation, manufacture, use and disposal. In addition, atrazine has been found in surface water and groundwater, as well as in drinking water wells, as a result of its application to crop fields as a preemergence herbicide. It has been detected in groundwater more frequently than any other pesticide (Dorfler et al. 1997; Koskinen and Clay 1997).

As a result of surface runoff from agricultural application and deposition by precipitation, atrazine is commonly found in streams, rivers, and lakes (Gaynor et al. 1995), salt marshes and their sediments (Meakins et al. 1995), and the ocean (Bester and Huhnerfuss 1993). It is found in higher concentrations in waters near high usage areas, such as the corn-belt in the upper midwest in the United States (Thurman et al. 1991).

6.2.3 Soil

Atrazine is widely used as a preemergence herbicide, and has been broadly applied to agricultural soils. It is commonly found in agricultural soils following application for several weeks to a few years. Atrazine may also be found in soils as a result of its formulation, manufacture, and disposal. According to the TRI, 501,732 pounds (227,582 kg) of atrazine were released to soil from four facilities that manufacture or process atrazine (TRI01 2003). Atrazine has been identified in soil and sediments in 7 and 6 of the 1,636 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 2003). According to Ribaudo and Bousahar (1994) 49,553,000 pounds (22,477,093 kg) of atrazine were used on 45,333,000 acres (18,346,014 hectares) of corn in the United States in 1993; the maximum reported usage was in 1976, when 90,340,000 pounds (40,839,154 kg) of atrazine were used in all agricultural applications.

6.3 ENVIRONMENTAL FATE

This section refers to the transport and partitioning of 2-chloro-4-ethylamino-6-isopropylamino-*s*-triazine, the major component in technical-grade atrazine and the primary component of most atrazine-containing herbicides. Please see Section 4.1, Chemical Identity, for a discussion of the few impurities documented in technical-grade atrazine. It is reported to only contain three classes of impurities, dichlorotriazines, hydroxytriazines, and tris(alkyl)aminotriazines. Little information is available on the fate of these impurities (HSDB 2001).

6.3.1 Transport and Partitioning

Atrazine has been detected in the atmosphere, both nearby and distant from areas where it has been applied as a pesticide. Based on its vapor pressure, atrazine will exist in both the particulate and vapor phases in the atmosphere, but should tend to exist more in the particulate phase than in the vapor phase. However, atrazine has been shown to volatilize from agricultural soils in the United States (Glotfelty et al. 1989; Weinhold and Gish 1994), and has been found in the vapor phase in the atmosphere (Chevreuil et al. 1996), in association with fog (Glotfelty et al. 1987) and rainwater (Bester and Huhnerfuss 1993; Trevisan et al. 1993; Wu 1981). In some monitoring studies, atrazine was found in the atmosphere only during the first month following the application of the herbicide to crops (Elling et al. 1987); in other cases, it was found 4 months (Chevreuil et al. 1996) to 8 months after application (Wu 1981).

The manner in which atrazine is applied to the fields may influence its volatilization to the atmosphere. Cumulative volatilization of atrazine from conventionally tilled fields was equal to 14% of the amount applied, but only 9% of the total applied was volatilized from no-till fields (Weinhold and Gish 1994). Air concentrations of atrazine vary with application season; concentrations usually range from just above the detection limit of ~0.03 ng/m^3 to more typical concentrations of 0.20–0.32 µg/m^3 (Trochimowicz et al. 2001).

Atrazine can be detected significant distances (100–300 km; 62–186 miles) away from the closest application area (Thurman and Cromwell 2000; Thurman et al. 1995) as a result of atmospheric transport. Atrazine is removed from the atmosphere by both precipitation and dry deposition, but precipitation is thought to be the primary mechanism for atrazine removal (Thurman and Cromwell 2000). In a study conducted in Germany, it was detected in 22–29% of precipitation samples collected over a 2-year period

(Siebers et al. 1994), with average concentrations ranging from 0.044 to 0.105 µg/L. In a study conducted on rainfall in the state of Iowa, 39% of 325 rainwater samples contained atrazine at concentrations ranging from 0.1 to 40 µg/L (Koskinen and Clay 1997). The average and median amounts detected were 0.91 and 0.34 µg/L, respectively. Atrazine concentrations ranged from <5 to 380 ng/L (median=50 ng/L) in rainfall collected from a rural site near Paris, France. In an urban collection area in Paris, the range was <5–400 ng/L (median also 50 ng/L) (Cheveuil et al. 1996). In a study of airborne dust samples from South Dakota, 50% of the collected samples contained atrazine or other triazine herbicides; concentrations of the total triazine herbicides in these dust samples ranged from 0.29 to 0.76 µg/g.

Atrazine can leach through the soil column and contaminate groundwater. When atrazine is deposited into aquatic matrices, some is expected to remain in the water column and some is expected to partition into the sediments. Atrazine has a measured log octanol/water partition coefficient (log K_{ow}) of 2.6–2.71 (Brown and Flagg 1981; Hansch et al. 1995) and has a solubility in water of 34.7 mg/L (Ward and Weber 1968). Atrazine has been shown to be relatively mobile in soils (Redondo et al. 1997; Southwick et al. 1995). In a silt loam soil, atrazine migrated almost as quickly at the conservative bromide tracer (Starr and Glotfelty 1990). Due to its high mobility, atrazine is commonly found in groundwater and as a contaminant of drinking water wells. In a study of groundwater sites in Iowa, atrazine was found in up to 41% of the 106 municipal wells tested in midwestern states (Kolpin et al. 1997a).

Experimentally-measured adsorption coefficients (log K_{oc}) for atrazine have been determined and range from 1.96 to 3.38. However, studies have not demonstrated a relationship between the measured log K_{oc} and organic matter content (Dousset et al. 1994; Koskinen and Rochette 1996; Weber 1991). This suggests that the adsorption of atrazine to soil is influenced by processes other than interactions with soil organic matter, such as interactions with clays or coatings on quartz minerals. Koskinen and Rochette (1996) observed this type of disparity between the K_{oc} of atrazine and soil moisture variations, and suggested that different types of interactions occur under different moisture regimes. Changes in the test conditions allowed for different interactions to occur between the atrazine and the clay minerals and soil organic matter. Wetting and drying cycles also enhanced the sequestration of atrazine in soil samples compared to those in which atrazine was exposed to continuous moisture (Kottler et al. 2001).

Following application to crop soils, most atrazine is found at the highest concentrations in the upper layers of soil, as a result of sorption (Koskinen and Clay 1997). Atrazine's rate of transport is dependent on many soil factors including the soil type, the amount of water that is applied to the soil, the presence of

crop residues, and the types of any fertilizers used. Soil pH may also affect the transport of atrazine. Atrazine sorption to soils increased with pH decreasing from 7.5 to 5.6 in a study of 10 Danish aquifer materials (Madsen et al. 2000). However, its mobility through soils, especially through macropores, has been demonstrated. In comparison to two other triazine herbicides (simazine and ametryn), atrazine was shown to be the most mobile in subtropical soils (Wang et al. 1996). Furthermore, the active ingredient of the applied herbicide moves more rapidly through soils than its breakdown products (Tasli et al. 1996). Its transport has been shown to occur along roots or through earthworm burrows (Koskinen and Clay 1997). In soils where mobile colloids are present, atrazine may be adsorbed and carried through preferential flow-paths in the soil and finally into groundwater (Sprague et al. 2000).

Atrazine transport varies from soil to soil, and laboratory experiments have suggested both significant and restricted movement of atrazine. In a study that examined of the effects of soil type, especially of sandy soils, on mobility, atrazine's mobility was higher in soils with higher hydraulic conductivities and less sorptive capacity (Wietersen et al. 1993). In contrast, in a soil column study, only small amounts of atrazine (~3%) were reported to leach in a sand or silt loam soil to a depth of 60–100 cm; most remained in the upper 15 cm of the soil (Koskinen and Clay 1997).

6.3.2 Transformation and Degradation

Atrazine is degraded slowly in most environments, whether by biological or chemical (e.g., photolysis) processes. Klint et al. (1993) observed no biodegradation of atrazine in groundwater or in groundwater combined with aquifer sediment systems, over a period of 539 days under anaerobic conditions. Anearobic degradation, however, was shown to occur under strongly reducing conditions by Seybold et al. (2001). Abiotic degradation of atrazine occurs by hydrolysis to hyrdroxyatrazine (2-hydroxy-4-ethyl-amino-6-isopropylamino-*s*-triazine), but this process is also very slow. Widmer et al. (1993) observed almost no hydrolysis of atrazine in typical groundwater over 19 weeks. No direct photolytic degradation has been detected in natural systems (Curran et al. 1992; Pelizzetti et al. 1990), but it is expected to undergo oxidation in the atmosphere in the presence of hydroxyl radicals, with an estimated half-life of 14 hours.

When atrazine is biodegraded, it is primarily biodegraded by dealkylation, where some organisms remove the ethyl moiety, forming deethylatrazine (2-chloro-4-amino-6-isopropylamino-*s*-triazine). Other microorganisms are effective at removing the isopropyl group, forming 2-chloro-4-ethylamino-6-amino-*s*-

triazine. Still others are capable of degrading atrazine through the formation of hydroxyatrazine. All of these transformations may lead to the complete degradation of atrazine, but this is not always observed. It is somewhat persistent in natural environments, as biodegradation slowly occurs in soils (Mandelbaum et al. 1993), sediments (Seybold et al. 1999), and surface waters (Feakin et al. 1994). In some cases, rather that being biodegraded, atrazine residues become incorporated into unextractable residues (Seybold et al. 1999), which are considered to be less bioavailable than the free parent or metabolite compounds. Seybold et al. (1999) showed that 2 years after exposure to atrazine, <2% of extractable atrazine or its metabolites remained in two different soil-based sediments.

6.3.2.1 Air

Atrazine has not been observed to undergo direct photolytic degradation in the atmosphere (Pelizzetti et al. 1990). It is, however, expected to undergo degradation in the atmosphere in the presence of hydroxyl radicals in the atmosphere. The half-life of atrazine is estimated to be 14 hours for a hydroxyl radical concentration of 5.0×10^5 OH^-/cm^3. It should be stated however, that this rate of photodegradation is expected for vapor-phase atrazine only; particulate-phase atrazine would not be expected to undergo photodegradation at this rate. This difference in atmospheric photodegradation rates is important since atrazine can be transported significant distances in the atmosphere. If atrazine existed primarily in the vapor phase in the atmosphere, a half-life of 14 hours would be expected to remove most of it from the atmosphere prior to deposition.

6.3.2.2 Water

Atrazine degradation in surface waters is slow, and its biodegradation in surface waters has not been demonstrably observed. It has been shown to have long residence times in the water column of lakes and streams, with half-lives >200 days. Photolysis of atrazine has not been demonstrated in water, unless substantial amounts of dissolved organic matter of acidic conditions are present (Curran et al. 1992; Penuela and Barcelo 2000). Atrazine degradation in surface waters appears to be primarily due to abiotic hydrolysis (Feakin et al. 1994), and losses from small streams were also best explained by an abiotic mechanism (Kolpin and Kalkhoff 1993). Biodegradation of atrazine has not been shown to occur in natural waters under aerobic conditions. Furthermore, no significant atrazine degradation has been observed under anaerobic conditions. Adrian and Suflita (1994) observed no anaerobic degradation of atrazine in aquifer slurries. No degradation of atrazine was observed in an alluvial gravel aquifer over a

distance of 90 m and a period of 49 hours. Atrazine concentrations were significantly reduced in batch tests over a period of 194 days; however, analysis suggests that the degradation is from chemical reduction and not biodegradation (Pang and Close 1999). Atrazine was degraded in the aqueous phase above anaerobic soil with a half-life of 86 days, under strongly reducing conditions (Seybold et al. 2001). Biodegradation has been shown only to occur when pure cultures of atrazine degraders are isolated from water or soil samples and grown in the laboratory; the activities of these organisms in the laboratory, however, have little or no relevance to natural aquatic biodegradation processes. Therefore, it appears that biodegradative losses of atrazine in aquatic systems are negligible.

6.3.2.3 Sediment and Soil

In a review of the fate of factors that affect atrazine persistence in soils of the United States, Kosikinen and Clay (1997) found that its removal half-life in soils ranged from 14 to 109 days, with a median half-life of 39 days. They acquired these half-lives from 15 field persistence studies of atrazine. It should be noted that in these determinations, disappearance of atrazine includes all mechanisms of removal including biodegradation, photolysis, volatilization, percolation into groundwater, and irreversible binding to soils. Most disappearance patterns were biphasic, with relatively faster disappearance occurring over the first few months following application, with slower disappearance kinetics occurring over the subsequent time period. Factors that were shown to affect the length of the half-life included soil type and the concentration of applied atrazine. Tillage practices had a slight influence on degradation, but this was not significant (Koskinen and Clay 1997).

Atrazine biodegradation in soils is relatively slow, with half-lives ranging from 4 to 57 weeks (Best and Weber 1974; Mandelbaum et al. 1993). It is somewhat persistent in natural environments, but biodegradation slowly occurs in soils (Mandelbaum et al. 1993) and sediments (Seybold et al. 1999). Atrazine disappearance has been demonstrated in soils, but its microbial mineralization is not commonly observed in soils. In a study of surface soils, Sinclair and Lee (1992) noted that even with long-term (12 years) exposure of soils to atrazine on treated roadsides, the indigenous microbes did not acclimate to atrazine, as atrazine was not biodegraded in soils collected from these sites. After 161 days, 80% of the added atrazine had disappeared from the surface soils, but there were no differences between the sterile and nonsterile soil treatments. Furthermore, atrazine was completely stable in all of the subsurface samples studied. Kruger et al. (1997) observed similar trends. No complete biodegradation (mineralization) of atrazine was observed in either saturated or unsaturated soils, at different depths over a

period of 120 days. Moderate amounts (5.8–66%) of the atrazine remained in the soils, depending on the amount of water saturation or depth of the soil. However, these amounts were no different from the amounts measured in sterile control soils, strongly suggesting that abiotic mechanisms were responsible for the degradation or loss of atrazine. Although no complete biodegradation was observed, degradation products were observed, including deethylatrazine and deisopropylatrazine. Half-lives calculated from the disappearance of atrazine ranged from 36 to 204 days in either the sterile or nonsterile soil.

Rodriguez and Harkin (1997) found slight, but insignificant degradation of atrazine in two different subsoils slurries over a period of over 270 days. Half-lives for atrazine were calculated to be 5.2 and 1.4 years in the different slurries. In a soil microcosm study, Dousset et al. (1997) observed no mineralization of atrazine in three different soils. Half-lives for the parent compound were calculated to be 66–105 days. In another study of the fate of atrazine in agricultural soils, atrazine had a half-life of 25–40 days in three nonsterile soils. In the control (sterilized) soils, atrazine had similar half-lives of 37–134 days (Qiao et al. 1996). Atrazine biodegradation was also measured in forest and grassland soils (Entry and Emmingham 1996). The authors found that after 30 days of incubation, atrazine was not degraded in the organic layer of grassland soils, and that only 1.2% degradation was observed in a mineral soil. More degradation was observed in the forest soils, with maximum amounts of mineralization (4.3%) observed in soil collected from a coniferous forest.

While little atrazine mineralization has been documented in soils, some studies have noted the formation of chlorinated derivatives of atrazine (Koskinen and Clay 1997; Kruger et al. 1997). Rodriquez and Harkin (1997) noted the formation of significant amounts of deethylatrazine (17.6%) and smaller amounts of deisopropylatrazine (2.7%) after 270 days in soils. Dousset et al. (1997) noted the formation of s-triazine derivatives following atrazine application, and 33–43% of these became incorporated into nonextractable soil residues.

Only a few studies have noted significant biodegradation of atrazine in soils. In a laboratory study, atrazine degradation in some soils was found to be concentration-dependent, with almost complete biodegradation of atrazine occurring within 20 weeks in a clay loam soil, at concentrations ranging from 5 to 5,000 mg/kg (Gan et al. 1996). By contrast, in a sandy loam soil, biodegradation was faster for the lower concentrations of atrazine in comparison to higher concentrations. At the highest concentration studied (5,000 mg/kg), however, no atrazine mineralization was observed in this soil. The authors did not supply a mechanistic explanation for the observed differences. Another study showed considerable and rapid atrazine mineralization in soil collected from the surface and subsurface of an agricultural site in

Ohio (Radosevich et al. 1996). In this study, relatively complete mineralization was observed within 50 days in soils collected from an area that has been historically exposed to atrazine. Atrazine mineralization half-lives in selected soils ranged from 3.4 to 43 days for surface soils, and from 17 to 43 days for subsurface samples. Mineralization was more rapid in soils collected near the surface as compared to those collected at depths >5 meters. The authors noted that some samples collected from this area (9 of 14) showed no mineralization of atrazine. The spatial variability in observed atrazine degradation led the authors to conclude that atrazine persistence in some soils was due to a lack of atrazine degraders in the soil, and not due to lack of appropriate nutrients or to unfavorable sorptive conditions (Radosevich et al. 1996). Ames and Hoyle (1999) argue that comparisons of bulk sediment parameters are useless for predicting biodegradation potential without knowledge of the distribution of atrazine-degrading microorganisms. In a study of atrazine biodegradation in 44 soil samples from a 3 ha contaminated agricultural chemical dealership, only samples from the southeastern corner showed biodegradation of atrazine. In most of these samples, atrazine was biodegraded to concentrations below detectable levels in 40 and 80 days, which was not predicted by sediment parameters.

Microorganisms (or groups of microorganisms) have been found that can degrade atrazine (Mandelbaum et al. 1993; Radosevich et al. 1995, 1996; Struthers et al. 1998; Wenk et al. 1998); the first isolation of a bacterium that could completely degrade atrazine, however, was not reported until 1995 (Radosevich et al. 1995). These strains have shown the capacity to degrade atrazine when added to soils contaminated with the pesticide, and have been developed for bioremediation applications in both soils and sediments. Crawford et al. (1998) showed that an atrazine-degrading bacterium could degrade atrazine under denitrifying conditions, and suggested that atrazine degradation occurred in indigenous lake sediments. However, no significant degradation occurred (approximately 0.5%) under these conditions. Therefore, while some bacterial strains can degrade atrazine in remediation applications, their activities should not be considered relevant to the environmental persistence of atrazine in soil. Atrazine has not been observed to undergo photolytic degradation in soils (Curran et al. 1992), nor abiotic hydrolysis in neutral pH groundwater when dissolved organic matter is present (Widmer et al. 1993). Atrazine was degraded in anaerobic soil with a half-life of 38 days under strongly reducing conditions (Seybold et al. 2001).

6.3.2.4 Other Media

The accumulation, persistence, and effects of atrazine have been measured in several other environmental media. These include oceans (Bester and Huhnerfuss 1993) and waste water treatment systems

(Nsabimana et al. 1996), as well as in animals (i.e., fish, tadpoles, invertebrates; see below) that inhabit freshwater environments.

In the ocean, atrazine has been measured at concentrations ranging from 1 to 100 ng/L (Bester and Huhnerfuss 1993), indicating that atrazine can be transported to the ocean, and that degradation during transport and residence there may not be rapid. In waste water treatment systems, atrazine has been shown to have little overall effect on treatment processes, but did tend to decrease microbial biomass.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

Atrazine has been observed in most air samples where it has been sought. In some cases, it has been detected only in rainwater. In a study conducted in Italy of the atmospheric fate of 12 different pesticides, atrazine was one of the most frequently detected herbicides in rainwater. In this experiment, atrazine was observed in 10 samples out of 146 collected (Trevisan et al. 1993). In the 10 rainwater samples that contained atrazine, its concentrations ranged from 0.15 to 1.99 μg/L, with a median concentration of 0.88 μg/L. These amounts fluctuated with the season, such that the highest concentrations were found around the month of June, following the earlier spring-time application of the herbicide to crops (Trevisan et al. 1993). These seasonal-based observations were similar to those of Bester and Huhnerfuss (1993) who noted higher atrazine concentration in rainwater during the months following application of the herbicide. In France, air concentrations of atrazine fluctuated depending on application season; concentrations usually ranged from just above the detection limit of ~0.03 ng/m^3 to more typical concentrations of 0.20–0.32 μg/m^3 in regions in and around Paris, France (Trochimowicz et al. 2001). In a study of airborne dust samples from South Dakota, 50% of the collected samples contained atrazine or other triazine herbicides; concentrations of the total triazine herbicides in these dust samples ranged from 0.29 to 0.76 μg/g (Muller et al. 1997).

Atrazine was detected in 70–96% of weekly rainwater samples taken from urban and agricultural sites in Mississippi, Missouri, and Iowa (Majewski et al. 2000). Positive weekly air samples ranged from 30 to 75% at urban sites and from 50 to 83% at agricultural sites (Foreman et al. 2000). Atrazine was detected in 76% of rainwater samples and 35% of air samples at a background site in Eagle Harbor, Michigan, indicating the potential for atrazine to undergo long-range transport. The concentration of atrazine in precipitation over Lake Michigan was found to be 0.10–0.40 μg/L during a study involving over

600 atmospheric samples (gas, particulate, and precipitation) from July 1994 to September 1995. Annual loading into Lake Michigan was found to be $1.04x10^3$ kg/year (Miller et al. 2000). Another study reported that the average atrazine concentrations monitored in the five Great Lakes from 1991 to 1995 are well below the U.S. Safe Drinking Water Act Minimum Contaminant Level of 3 µg/L and the Canadian Aquatic Life Criteria of 2 µg/L (Tierney et al. 1999).

The difference between atrazine concentrations in urban and rural air was emphasized in a study that compared rainwater and air samples from the urban area of Jackson, Mississippi with samples from the agricultural region of Rolling Forks, Mississippi (Coupe et al. 2000). Atrazine was detected in 69% of rainwater samples from Jackson with a median concentration of 0.006 µg/L compared to 75% of rainwater samples from Rolling Forks with a median concentration of 0.02 µg/L. Atrazine was detected in 29% of particulate samples from Jackson with a median concentration below the detection limit compared to 67% of particulate samples from Rolling Forks with a median concentration of 0.058 ng/L. Atrazine was detected in 42% of gas samples from Rolling Forks with a median concentration below the detection limit. Atrazine was not detected in gas samples taken from Jackson.

6.4.2 Water

In a study of atrazine distribution to several bodies of water in the northern midwestern United States, atrazine was consistently detected in samples collected before crop planting, shortly thereafter, and at harvest time. Atrazine concentrations, however, fluctuated considerably. It was detected in 91% of surface water (river and stream) samples that were collected before crops were planted, and in 98% of water samples collected after the crops were planted. Following the growth season (at harvest), it was detected in 76% of the collected water samples. In a similar set of monitoring studies in Canada, atrazine was detected in 80% of the agricultural watershed streams that were sampled. In this study, concentrations were measured in streams in 11 different agricultural watersheds (Frank et al. 1982). The highest concentration that was detected was 33 µg/L, with the average concentrations ranging from 1.1 to 1.6 µg/L. Mississippi River samples collected at Baton Rouge, Louisiana from 1991 to 1997 contained atrazine with a median concentration of ~0.45 µg/L (Clark et al. 1999). The flux of atrazine in the Mississippi River at Baton Rouge, Louisiana from January 1996 through September 1997 was 963 metric tons. All 129 samples taken from 75 Midwestern streams and rivers in 1998 contained atrazine (Battaglin et al. 2000). The median and maximum concentrations were 3.97 and 224 µg/L, respectively. Atrazine was detected at 14 out of 25 groundwater sites in the same region. Median and maximum concentrations

were 0.010 and 0.410 µg/L, respectively. The USGS analyzed 2,485 sites from 20 of the nation's major hydrologic basins for pesticides from 1992 to 1996 during the USGS National Water Quality Assessment Program (Kolpin et al. 2000). Atrazine was found in 30% of the samples with a maximum concentration of 4.20 µg/L. Atrazine was detected with a concentration of 5.06 µg/L in samples from flood waters of the Nishnabotna River in Southwest Iowa (USGS 2000). This flood took place in June 1998, shortly after chemical application associated with planting of crops.

Concentrations of atrazine in surface waters that are impacted by agricultural use tend to fluctuate with the season, with the highest atrazine concentrations being observed in the weeks and months following application of the herbicide (Albanis et al. 1998; Battaglin and Goolsby 1999). Since atrazine is a preemergence herbicide, these detections would occur prior to planting and shortly thereafter. For example, atrazine was detected in 91% of 55 surface water (river and stream) samples that were collected before crops were planted, and in 98% of 132 water samples collected within 2 weeks of crop planting. Following the growth season (at harvest), it was detected in only 76% of 145 of the water samples collected (Thurman et al. 1991). These observations show that atrazine was consistently detected in these water samples early in the growth season, but it should be noted that the concentrations of atrazine fluctuated considerably. The samples collected after the crops were planted contained an order of magnitude higher concentrations (median concentration ≈4 µg/L) than either the preplanting or harvest samples, which had median concentrations of approximately 0.4 µg/L. In a similar set of monitoring studies in Canada, atrazine was detected in 80% of the agricultural watershed streams that were sampled. In this study, concentrations were measured in streams in 11 different agricultural watersheds (Frank et al. 1982). The highest concentration that was detected was 33 µg/L, with the average concentrations ranging from 1.1 to 1.6 µg/L.

To address the amounts of atrazine that reach streams as a result of agricultural runoff, studies have been conducted to investigate the concentrations of atrazine in surface runoff following application (Gaynor et al. 1995). Atrazine concentrations in surface runoff were greatest following application of the herbicide to the fields, and it was found that the concentrations varied according to the agricultural practice used. The highest maximum amount of atrazine observed in surface runoff, 700 µg/L, occurred when the fields were managed by a no-till cultivation practice; lower maximum surface runoff concentrations were observed (400 µg/L) when conventional tillage was used. It should be noted that in the receiving streams, atrazine concentrations were about 10-fold lower than surface runoff concentrations. This difference was a result of sorptive and other losses that occurred prior to the surface runoff reaching the surface bodies of water (Gaynor et al. 1995), not simply dilution into the larger amount of receiving waters. It should be

noted that the amounts of atrazine lost by volatilization from no-tillage fields vs. conventional tillage fields contrast with runoff observations. Following application of atrazine to conventional tillage fields, up to 14% was volatilized. Less atrazine volatilization (9%) was observed following application to no-tillage fields (Wienhold and Gish 1994). Leaching after a heavy rainfall was reported to hinder the volatilization of atrazine in freshly tilled soil (Rice et al. 2002). Atrazine loss due to volatile fluxes was 7.5% after 20 days, with 59% of the loss occurring within 4 days of treatment.

Based on a 5-year National Survey of Pesticides in Drinking Water Wells (NPS), the EPA estimated that atrazine was present in 1,570 CWS wells nationwide (EPA 1990a). Due to the statistical nature of the estimation calculation used, the estimates range from a low of 420 to a high of 2,701 CWS wells. The EPA also estimated that there are 70,800 rural domestic wells contaminated with atrazine (estimates range from a low of 13,300 to a high of 214,000) (EPA 1990a). The estimates assume only that the concentration of atrazine would be above the limits of detection (0.12 µg/L) used in the survey. However, the maximum atrazine concentration detected in a CWS well was 0.92 µg/L; the maximum concentration detected in a rural domestic well was 7.0 µg/L (EPA 1990a). A more recent report found maximum seasonal and annual average concentrations of atrazine plus chlorinated metabolites to be 61.6 ppb and 18.9 ppb, respectively, during a 1993–1998 monitoring program of 13 CWS in the United States that use surface water (EPA 2002a). Atrazine is generally found at higher concentrations in CWS that use surface water sources compared to those that use groundwater sources.

In a study in Maine, atrazine was detected in 18 out of 58 (31%) drinking water wells. Most wells contained <0.6 µg/L atrazine, but two contained atrazine at concentrations >3 µg/L (Bushway et al. 1992). In a study of groundwater underneath irrigated farmland in central Nebraska used primarily for growing corn, atrazine was detected in all of the 14 wells tested (Spalding et al. 1980). Concentrations in these wells ranged from 0.06 to 3.12 µg/L, with an average concentration of 0.75 µg/L (Spalding et al. 1980). In a study of groundwater sites in Iowa, atrazine was found in 41% of the 106 municipal wells tested in 1995 (Kolpin et al. 1997a), in 4.4% of 686 rural wells examined during 1988–1989, and in 12% of 355 groundwater monitoring wells during 1982–1987. In a broader study of groundwater quality in Iowa, 209 (19.5%) of 1,485 wells tested contained atrazine at concentrations above 0.1 µg/L (Kolpin et al. 1997b). The amounts of atrazine found in wells in Iowa remained relatively constant from 1982 to 1985, reflecting the constant usage of atrazine in Iowa agriculture (Kolpin et al. 1997b). In contrast, a survey of 103 randomly-chosen farmstead wells in Kansas found that only 4 were contaminated by atrazine (Steichen et al. 1988). The concentrations detected were higher, and changed with season. The highest detected atrazine concentration was 7.4 µg/L during the winter. When these wells were sampled again

during May or June, an even higher maximum concentration of atrazine, 40 µg/L, was detected. It was proposed that the higher levels observed in the spring months reflected usage patterns that had occurred prior to sampling. It should be noted that this study had a relatively high detection limit for atrazine of 1.2 µg/L (Steichen et al. 1988).

Atrazine is also commonly found in other bodies of water such as man-made canals (Miles and Pfeuffer 1997), estuaries (Wu 1981), and lakes (Muller et al. 1997). Triazine herbicides, including atrazine, were the most commonly-detected pesticides in a 5-year monitoring study of 27 water sampling stations in canals found in southern Florida. In these canals, atrazine represented 37% of all pesticide detections, and was present in the water at concentrations up to 18 µg/L (Miles and Pfeuffer 1997). As in other studies (e.g., surface runoff monitoring studies), atrazine was detected primarily in the months around application in the spring. Similar observations of atrazine concentration fluctuations were noted for the Rhode River estuary in Maryland. Wu (1981) measured atrazine concentrations in this estuary for over 2 years. However, atrazine was present in the estuary waters all year, and ranged in concentration from 0.006 to 0.19 µg/L. In a longer-term (5-year) study of atrazine in three Swiss lakes, Muller et al. (1997) found that the amount of atrazine was very dependent upon the amount of rainfall that occurred during the application period, and transport to the lake was dominated by rainfall, not surface runoff. This was suggested by the observation that while the three lakes had very different cachement areas and hydraulic properties, atrazine deposition was relatively uniform in each lake receiving similar amounts of rainfall. It was estimated that total inputs into the lakes reflected 0.5% of the soil-applied atrazine in a dry application period to up to 2% of the soil-applied atrazine during a wet (rainy) application period (Muller et al. 1997).

6.4.3 Sediment and Soil

Atrazine residues vary in soils, depending on usage and exposure to climatic patterns that may lead to atrazine deposition. In soils, atrazine has been found at high concentrations resulting from applications. Atrazine is moderately persistent in surface soils. Its concentrations in soils have been shown to slowly decline over a periods of 12 months in surface soils, from 0.83 µg/g 6 days following application of 1.1 kg/ha, to 0.5 µg/g 2 months following application, to 0.08 µg/g 12 months following application (Frank and Sirons 1985). Similar trends of disappearance were observed when it was applied at concentrations of 2.2 or 3.3 kg/ha (Frank and Sirons 1985); in all cases, concentrations had dropped by approximately 90% over a period of 1 year. Regardless of the application rate, atrazine had a half-life of

approximately 3.3 months in the soils (Frank and Sirons 1985). The initial atrazine concentration in sandy loam samples taken from a plot sewn with maize was 0.670 mg/kg (Konda and Pasztor 2001). This concentration decreased to 0.376 mg/kg (56.2%) after 14 days and 0.242 mg/kg (36.1%) after 28 days. Only 1.37% of the initial concentration of atrazine was detected after 140 days. Atrazine levels were also monitored in agricultural soil plots in Minnesota, which showed slightly different trends. Levels of atrazine in the surface layers (0–10 cm depth) of a sandy loam soil dissipated (disappeared or leached) over the 13-month study (Gan et al. 1996). In one test in this study, a high concentration of atrazine, representing a spill event (6.3 g/kg), was applied to the soil and its concentrations monitored over 13 months. At the end of the monitoring period, only 0.13 g/kg remained in this soil layer. When normal application concentrations (7.2 mg/kg) were applied to the same soil, however, dissipation was slower, and after 13 months, concentrations had only been reduced to 2.3 mg/kg. Similar trends were observed in a clay loam soil, but dissipation was somewhat faster and more uniform in the clay loam soil as compared to the sandy loam soil (Gan et al. 1996). A complimentary study examined atrazine dissipation in three agricultural soils from Germany. In all soils, atrazine levels decreased in a relatively linear fashion from approximately 5.5 to 1 mg/kg over 110 days. There was very little difference in the rates of atrazine dissipation between soils that were autoclaved and those that were not, especially for acidic soils. In alkaline soils, atrazine dissipation was somewhat faster in the natural soils, showing that microbial metabolism had an influence on atrazine fate. Therefore, concentrations of applied atrazine are not static in soils, but will tend to decline over time. It appears that for neutral to acidic soils, these dissipation processes can be primarily abiotic.

6.4.4 Other Environmental Media

Atrazine has been detected in oceans, at concentrations ranging from 1 to 100 ng/L and in estuaries at concentrations of 200 ng/L (Bester and Huhnerfuss 1993). Concentrations were generally higher closer to shore, and the monitoring study demonstrated that the Elbe River estuary, located in Germany, is highly contaminated with atrazine.

In fish, atrazine had a bioconcentration factor (BCF) of <10 in *Leuciscus idus* (golden orfe), after a 3-day exposure. In *Cyprinus carpio* (common carp), the measured BCF was 3–4 in some tissues (liver, kidney, and intestine) but only 1 for blood, muscle, and gills (Gluth et al. 1985). This suggests that atrazine does not bioaccumulate to a high degree in fish (Gluth et al. 1985). It has not been shown to bioaccumulate nor to be toxic to *Daphia magna*, at 10 µg/L (Baun and Nyholm 1996). BCF values measured for

D. magna in natural water were low, ranging from 2.4 to 3.0 (Akkanen et al. 2001). No toxic effects of atrazine were observed in *D. magna*, fathead minnows (*Pimephales promelas*), or tadpoles (*Rana pipiens*) in wetland mesocosms, at atrazine concentrations up to of 25 µg/L (for daphnia and tadpoles) or 75 µg/L (minnows) (Detenback et al. 1996).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

According to the United States National Occupational Exposure Survey performed between 1981 and 1983 (NIOSH 1989), approximately 1,000 chemical industry workers, 123 of which were female, were potentially exposed to atrazine. Occupational exposure may occur through dermal exposure or inhalation exposure during the manufacture, formulation, and application of atrazine.

A study in Maryland examined pesticide metabolite concentrations in 80 randomly selected individuals from five counties. Exposure was evaluated by analysis of urine samples, and for atrazine, the presence of atrazine mercapturate (the primary excretory metabolite of atrazine) was evaluated. This metabolite was detected in only one sample out of the 348 total samples collected. In a similar study, 0.19% of 529 adults from the National Human Exposure Assessment Survey tested positive for atrazine mercapturate in urine samples (Needham et al. 2000).

FDA's Total Diet Study (TDS) has provided data on dietary intake of food contaminants for almost 40 years (FDA 2000b). It was initiated in 1961 as a program to monitor radioactive contamination in foods following atmospheric nuclear testing. Since then, it has been enlarged in scope to also monitor pesticides, industrial chemicals, toxic and nutritional elements, and vitamin residues in food. The analyses have been performed on foods that have been prepared for consumption, making the final results most relevant for a realistic estimate of dietary intake.

Even though atrazine is a widely used pesticide for corn and sugarcane, no atrazine residues were found in 16,648 samples of foods tested between 1991 and 1992 (IARC 1999) where a reporting limit of 50 µg/kg was used. Atrazine was found in residues of an unspecified number of foods in FDA analyses in only two of the years from 1993 to 1999 (FDA 1993, 1994, 1995b, 1996, 1997, 1998, 1999). In these analyses, atrazine was found in an unspecified number of foods in 1997 and 1999, but not in 1993, 1994, 1995b, 1996, or 1998. A recent FDA Total Diet Study (FDA 2000a) reported atrazine only in a roasted chicken sample at a concentration of 1 µg/kg. Similarly, the 1998 USDA Pesticide Data Program

reported that atrazine was not found in any of 6,643 fruit or vegetable samples, 585 milk samples, or 298 samples of corn syrup (USDA 1998). Limits of detection in these cases ranged from 0.01 µg/g or 0.01–0.33 µg/mL. In 1999, the same report noted that out of 6,419 fruit and vegetable measurements, atrazine was only detected once in a frozen spinach sample at a concentration of 0.028 µg/g. However, it was not detected in 156 analyses of corn syrup, where the limit of detection was 0.002 µg/mL (USDA 1999). These data suggest that most members of the general population have little or no exposure to atrazine from foods. In a study conducted in Germany, no atrazine was detected in several foods above allowable limits, when analyzed by a dipstick immunoassay approach (Wittmann et al. 1996). In these assays, allowable atrazine concentration limits were 10 mg/kg for mushrooms, spices, coffee, and tea; 1 mg/kg for sweet corn; 0.5 mg/kg for corn; and 100 µg/kg for other foods (Wittmann et al. 1996). In all samples analyzed, concentrations were below the detection limit of 0.3 µg/L, except for black aromatized tea, which had an atrazine concentration of 0.9 µg/L.

Drinking water analysis of agroecosystems in Ontario, Canada, for the years 1987–1991 showed atrazine concentrations ranging from 0.05 to 0.65 µg/L, with an average water concentration of 0.162 µg/L and a median concentration of 0.126 µg/L (Van Leeuwen et al. 1999).

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 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).

Even though children are exposed to a wide variety of chemicals, including atrazine, there is a lack of information from which to estimate their exposure (Quackenboss et al. 2000) to pesticides. It is expected,

however, that since children, due to their behavior and lifestyle, will be exposed to atrazine as a result of food preparation and their types of activities. Babies that are fed formula may be exposed to atrazine in drinking water due to their formula being reconstituted with drinking water collected from contaminated wells, as well as in their normal drinking water consumption. In addition, children may be exposed to atrazine from home and outside play activities. These would be as a result of playing on indoor floors that may have atrazine-containing dusts, or in yards or play areas outside that may contain atrazine.

A multipathway exposure assessment evaluated exposure of pesticides to children 3–12 years of age in the Minnesota Children's Pesticide Exposure Study (MNCPES), which was a project designed to acquire exposure information for children for a variety of pesticides, including atrazine (Quackenboss et al. 2000). This assessment sought to address multipath exposures from air, water, food, soil, and residential surfaces in the homes of the children. The study was designed to assess a wide range of households, so that different types of living conditions (rural vs. suburban households) could be compared and evaluated. A summary of the design strategy and implementation success (Quackenboss et al. 2000) reported that all samples had been collected and have been chemically analyzed, and the data were undergoing initial statistical analyses. Initial results from that study (Lioy et al. 2000) have shown that most atrazine is transported into the home by an unquantified and unidentified transport mechanism, thought to be tracking of soil into the home on shoes and feet (Lioy et al. 2000). Analysis of the home environment showed that it was present in 62 of 102 surface samples of the homes, in 61 of 102 carpet samples, and in 12 of 100 children hand rinse samples, but only in 2 of 89 of the urine samples collected from the children in the study. Ranges of atrazine in the homes ranged from 0.04 to 6.5 μg/mL of the samples collected from the surfaces (expressed in terms of uniform amounts of solution used to extract the sampling material). The relatively common occurrence of atrazine (in more than half of the environmental samples) show that children may be exposed to atrazine. Initial analysis of the urine samples, however, showed rare occurrence within potentially exposed children, as only 2 of 89 children had detectable levels of atrazine in the urine with concentrations ranging from 0.6 to 22 μg/g creatine (Lioy et al. 2000).

However, recent reports have suggested that more data are needed. According to a Federal Insecticide Fungicide and Rodenticide Act (FIFRA) report on the hazard and dose-response assessment of atrazine (Dorsey and Portier 2000), there are not enough data on the risk of atrazine to children, because exposure data are not available.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Populations with potentially high exposures include pesticide, manufacturing, and railway workers. Data, however, exist mainly for pesticide workers (IARC 1999). Denovan et al. (2000) studied the levels of atrazine exposure in herbicide appliers by monitoring concentrations in saliva. Fifteen male pesticide appliers were invited to take part in the analysis through NIOSH screening procedures. Saliva concentrations of atrazine were significantly higher on the days that the herbicide was applied, in comparison to the days when it was not applied. Salivary concentrations were shown to peak in the afternoon (between 4 and 6 pm) of the day that the atrazine was sprayed, but concentrations decreased by bedtime, and were further reduced by the next morning. Based on observed deviations between subjects, saliva concentrations of >10 μg/L were determined to be a plausible predictor of an atrazine exposure. While concentrations of atrazine were higher in the samples collected at the end of the work day, atrazine concentrations in the saliva the morning following application were not statistically different from concentrations on nonspray days, but were approximately twice that of the preseason atrazine saliva concentrations. The median preseason concentration of 0.9 μg/L saliva may represent normal background exposure concentrations, since these samples were collected 1 month before the spraying season, or they could represent elimination of fat-stored atrazine. Alternatively, they could indicate low-level exposure to atrazine during work near atrazine-contaminated surfaces at the workplace (Denovan et al. 2000).

Other studies conducted on Italian herbicide workers (Catenacci et al. 1990) and on Finnish railway workers (Ikonen et al. 1988) demonstrated that urinary atrazine concentrations correlated with atrazine concentrations in the air during the work shift, and that the highest amounts of atrazine or atrazine metabolites in the urine were excreted either during or immediately following the exposure. A second study of Italian herbicide workers, however, showed no correlation between ambient air concentrations and urinary excretion concentrations (Catenacci et al. 1993). Differences were determined to be related to the differential dermal exposure of some workers to atrazine. Worker exposure was estimated to range from $4x10^{-6}$ mg/kg/hour for an enclosed cab ground applicator applying atrazine to sorghum, up to a high of $1.6x10^{-3}$ mg/kg/hour for mixer/loader applicators working on open cab applicators on Florida sugar cane (IARC 1999; Lunchick and Selman 1998).

As noted in Section 6.4.2, based on a 5-year NPS, the EPA estimated that atrazine was present in 1,570 CWS wells nationwide (EPA 1990a). Due to the statistical nature of the estimation calculation used, the estimates range from a low of 420 to a high of 2,701 CWS wells. The EPA also estimated that there are 70,800 rural domestic wells contaminated with atrazine (estimates range from a low of 13,300 to

a high of 214,000) (EPA 1990a). The estimates assume only that the concentration of atrazine would be above the limits of detection (0.12 µg/L) used in the survey. However, the maximum atrazine concentration detected in a CWS well was 0.92 µg/L; the maximum concentration detected in a rural domestic well was 7.0 µg/L (EPA 1990a). A more recent report found maximum seasonal and annual average concentrations of atrazine plus chlorinated metabolites to be 61.6 and 18.9 ppb, respectively, during a 1993–1998 monitoring program of 13 CWS in the United States that use surface water (EPA 2002b). It is noted that atrazine is generally found at higher concentrations in CWS that use surface water sources compared to those that use groundwater sources.

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 atrazine 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 atrazine.

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 atrazine are sufficiently well defined to allow assessments of the environmental fate of atrazine to be made (Bailey et al. 1968; Brown and Flagg 1981; Dousset et al. 1994; Green et al. 1993; Hansch et al. 1995; HSDB 2002; Humburg 1999; IARC 1999; Koskinen and Rochette 1996; Meakins et al. 1995; Reiderer 1990; Tomlin 1997; Verschueren 2001; Ward and Weber 1968; Weber 1991), and no additional information is needed.

Production, Import/Export, Use, Release, and Disposal. Information is needed that provides more recent estimates or actual values for quantities of atrazine that are produced, imported, and exported, as well as more data on the amounts used in agriculture and other weed-control applications.

Environmental Fate. The fate of atrazine has been well-studied and reviewed in the current literature. Due to its widespread usage, it is one of the best studied pesticides (IARC 1999; Koskinen and Clay 1997); however, biodegradation has rarely been documented in soils or in groundwater, suggesting that indigenous microorganisms that degrade atrazine are lacking. Since atrazine is observed to undergo degradation in some soils, more environmental fate studies are needed to determine the factors and mechanisms that permit degradation in these soils compared to soils where it is not observed. In addition, to better understand how atrazine interacts with the soil environment, more research is needed to determine the nature of the sorptive interaction(s) between atrazine and the particulate and chemical environment of different soils. This will provide either an explanation of the relatively wide range of observed K_{oc} values, or it may provide a better estimate of its true K_{oc}.

Bioavailability from Environmental Media. No additional information on the bioavailability of atrazine from environmental media is warranted at this time.

Food Chain Bioaccumulation. Little food chain accumulation of atrazine has been observed, as it does not tend to bioaccumulated; thus, no additional data are needed.

Exposure Levels in Environmental Media. No additional information on exposure levels of atrazine in environmental media is warranted at this time.

Exposure Levels in Humans. Due to the widespread usage of atrazine, but lack of toxicological effects, more data are needed to verify whether exposures to atrazine can lead to toxicological effects. Most exposure level evaluations have occurred in applicators; more data are needed for farmers.

Exposures of Children. There is current research evaluating pesticide exposures to children in Minnesota. However, more data are needed, as is indicated in the FIFRA report on the hazard and dose-response assessment of atrazine (Dorsey and Portier 2000). This research should yield valuable information regarding childhood atrazine exposures in the near future.

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

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2002) database and the Current Research Information System (CRIS 2002) provide additional information obtainable from ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-2. The successful completion of these projects will contribute to better understanding of environmental fate of atrazine, a better set of approaches to study the fate of atrazine in environmental matrices, and a better set of agricultural practices that could reduce the levels of atrazine exposure to humans.

Research planned by the EPA will involve monitoring of triazines and their degradation products (including atrazine) in drinking water as prescribed by the Safe Drinking Water Act (SDWA) for chemicals on the Contaminant Candidate List (CCL). EPA will use these data to determine if further regulation is required for these chemicals according to the SDWA.

Table 6-2. Ongoing Studies on the Potential for Human Exposure to Atrazine

Investigator	Affiliation	Research description	Sponsor
Bleam W	University of Wisconsin, Madison, Wisconsin	Analysis of hydrogen bonding of atrazine by NMR approaches. Goal is to better describe interactions of atrazine with soil organic matter.	National Center for Research Resources
Camper ND, Riley MB	Clemson University, Clemson, South Carolina	Evaluation of SPE approaches for improving extraction of and stabilization of pesticides from water samples. Sampling and approaches were tested, and stability of environmental samples was shown to be better when shipped in SPE matrices as compare to shipment of water samples. Should lead to better accuracy of determinations of pesticides in aquatic matrices.	Hatch award
Currie RS	CSREES, Kansas	Evaluation of registered and experimental herbicides in replicated experiments for weed control and crop tolerance. Weed control tactics will be developed that integrate cultural, mechanical, and chemical weed control methods. Biological, physiological, and ecological characteristics of some major weed species and the interactive affects in crops will be studied.	Hatch
Grichar WJ	Texas A&M University, College Station, Texas	Develop cultural practices that increase soil stability, reduce wind and water erosion. Found that some combinations of atrazine with other pesticides (pendimethalin) resulted in stunted grain sorghum growth.	Hatch
Griffin JL	Lousiana State University, Baton Rouge, Louisiana	Determine efficacy of pre- and post-emergence herbicides on common weeds in southern Louisiana crops. Found that weeds common in sugar cane crops were not resistant to atrazine, but that the atrazine was not commonly applied at the correct time for control of this weed.	Hatch
Huang H-M	Jackson State University, Jackson, Mississippi	Examination of the relative and combined roles of photolysis and microbial degradation on the fate of atrazine in surface waters, as well as to assess mutagenicity or toxicity of reaction products.	National Institute of General Medical Sciences
Johnston CT	CSREES, Indiana	Development of improved models to predict pesticide fate and transport in soils based on soil sorption data.	Hatch
Leidy RB	North Carolina State University, Raleigh, North Carolina	Development of SPE approaches for collection and stabilization of pesticides from water samples. Research will try to demonstrate that the SPE disks improve stability of sample during transport (over shipment of water samples), and will result in less error between test labs.	Hatch
Leidy RB	North Carolina State University, Raleigh, North Carolina	Validate methods for analyses conducted with 3M Empore disc membranes for pesticides including atrazine.	Hatch

Table 6-2. Ongoing Studies on the Potential for Human Exposure to Atrazine

Investigator	Affiliation	Research description	Sponsor
Montvaldo R et al.	University of Puerto Rico, Mayaguez, Puerto Rico	Evaluation of SPE approaches for sampling water for pesticides. Testing of sample showed excellent recoveries of test pesticides. Will lead to better analysis of pesticides in field samples by minimizing transportation and storage losses.	Hatch
Mueller TC	University of Tennessee, Knoxville, Tennessee	Evaluation of SPE approaches for stabilization of pesticides in water. Research demonstrated that the SPE approaches improved pesticide stability during transport.	Hatch
Nkedi-Kizza P	SAES, Florida	Examination of the influence of physical, chemical, and mineralogical soil properties that influence the fate and transport of organic pesticides in the environment.	State
Pignatello JJ, Xing B	CSREES, Connecticut	Investigation of the causes of “non-ideal” sorption and development of experiments to further test a previous hypothesis that soil organic matter behaves like a glassy polymer in regard to its sorptive properties.	Cooperative agreement
Radosevich M et al.	CSREES, Delaware	Investigation of the link between the diversity, frequency, and expression of genes encoding the atrazine degradative pathway and observed aerobic and anaerobic degradation rates in environments with and without a prior history of atrazine application.	NRI
Senseman SA	Texas A&M University, College Station, Texas	Investigation of the environmental fate of herbicides in water, soil, and plants by evaluation of runoff, sorption, and degradation of herbicides in different environmental compartments. Examined SPE extraction, along with supercritical fluid extraction from samples.	Hatch
Sims GK, Wax LM	Agricultural Research Service, Illinois	Identification of mechanisms of herbicide persistence associated with carryover damage and offsite movement. Study of the susceptibility of weed seeds to microorganisms during seed decay, the role of microbial inhibition in biodegradation of herbicides with anti-microbial properties. Exploration of practical approaches to enhance degradation of xenobiotics used in agricultural production.	USDA
Spalding RF	CSREES, Nebraska	Examination of the impact of management alternatives on groundwater and surface water quality and development of *in situ* aquifer methods to remediate groundwater nitrate concentrations.	Hatch
Yoder RE et al.	University of Tennessee, Knoxville, Tennessee	Investigation of agricultural production systems that minimize off-site movement of pesticides. Monitored surface flow, developed better surface maps, and analyzed these to better predict surface solute transport. Monitored atrazine surface and soil transport.	Hatch

Table 6-2. Ongoing Studies on the Potential for Human Exposure to Atrazine

Investigator	Affiliation	Research description	Sponsor
Zhu KY	CSREES, Kansas	Elucidation of chemical and biochemical mechanisms and pathways of pesticide residue degradation including characterization of degradation products. Characterization and quantification of exposure and effects of pesticides and their degradation products on target and nontarget organisms.	Hatch

[a]Source: CRIS 2002; FEDRIP 2002

CSREES = Cooperative State Research, Education, and Extension Service; NMR = Nuclear Magnetic Resonance; NRI = National Research Institute; SPE = solid phase extraction; USDA = U.S. Department of Agriculture

7. ANALYTICAL METHODS

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

Atrazine can be detected in mammalian biological samples, as well as in foodstuffs related to human consumption. It has been detected in human saliva (Denovan et al. 2000), skin (Lioy et al. 2000; Lorberau and Pride 2000), plasma and organ tissues (Pommery et al. 1993), liver samples (Lang et al. 1996), and urine (Ikonen et al. 1988; MacIntosh et al. 1999) using gas chromatography (GC), high performance liquid chromatography (HPLC) (Buchholz et al. 1999), and enzyme-linked immunosorbent assay (ELISA) methods (Trochimowicz et al. 2001). A summary of various methods is supplied in Table 7-1.

Human tissue or other samples suspected of containing atrazine are usually extracted from the tissue or fluid sample prior to analysis. For urine analysis, urine samples can be extracted with diethyl ether. This solvent is recovered and combined with ethyl acetate. The ethyl acetate fraction is evaporated to a smaller volume and analyzed by GC (Ikonen et al. 1988). For liver tissue microsomes, the material is extracted with a solvent, such as dichloromethane (Lang et al. 1996), which is then evaporated. The residue containing the atrazine or its metabolites is dissolved in acetonitrile and analyzed by HPLC. For saliva samples, the material is simply centrifuged and then is used directly for ELISA analysis (Denovan et al. 2000).

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	The sample is first amended with saturating amounts of sodium chloride, then extracted with two volumes of diethyl ether; ether layer recovered and extracted with ethyl acetate (this was reduced to 1/5 its volume by evaporation)	GC	1 µg/L	Not reported	Ikonen et al. 1988
Plasma, organ tissues	Blood collected in heparinized tubes, centrifuged; plasma stored at -20 °C; atrazine was extracted from plasma with dichloromethane, evaporated to dryness under N_2, washed with acid and base, then dissolved in mobile phase (40% water; 60% methanol)	HPLC	14.25 ng/g	58–61%	Pommery et al. 1993
Saliva	Saliva collected on a cotton sampler (Salivette); the sampler is centrifuged, and cotton material removed, leaving the filtrate; sample used directly	ELISA	0.22 µg/L	Not reported	Denovan et al. 2000
Liver microsomes	The sample is extracted with dichloromethane, and then evaporated; the residues are dissolved in acetonitrile/aqueous KOH (5 mM)	HPLC-UV	2–5 pmol	96–103%	Lang et al. 1996
Food	EPA-approved method 4670 for drinking water that has been used for food; sample is minced or liquified, then filted and brought to neutral pH; then followed by proprietary ELISA method	ELISA	0.1 µg/L	Not reported	SDI 1999
Eggs	Supercritical fluid (carbon dioxide) extraction of eggs, followed by hexane and benzene in acetone elution, followed by GC-NPD analysis	HPLC	100 µg/kg	90.4%	Pensabene et al. 2000
Hand (dermal) contamination	Hand washed in 150 mL of isopropanol in a polyethylene bag for 30 seconds. Solution transferred to a glass jar; 10 mL removed from jar, derivatized in diazomethane derivitizing agent, silicic acid is added, followed by sample filtration and analysis by GC-ECD	GC-ECD	0.01 µg/mL	87.1–103%	NIOSH 1998b

ECD = electron capture detection; ELISA = enzyme-linked immunosorbent assay; EPA = Environmental Protection Agency; GC = gas chromatography; HPLC = high performance liquid chromatography; UV = ultraviolet

7.2 ENVIRONMENTAL SAMPLES

Atrazine can be determined in environmental samples using chromatographic, spectroscopic, and immunogenic methods. Standard EPA methods include Infrared spectroscopy, GC separation with flame ionization detection, and HPLC with detection at 254 nm (ultraviolet [UV]) (Stafford et al. 1992). Different GC methods have been used for atrazine detection and quantification and include GC coupled with a flame ionization detector (FID) (IARC 1999), GC coupled with an electron capture detector (ECD) (Albanis et al. 1998; Lopez-Avila et al. 1992; Trevisan et al. 1993; Walker and Porter 1990), GC coupled with a nitrogen-phosphorus detector (NPD) (Albanis et al. 1998; Amistadi et al. 1997; Ferrari et al. 1998; Mojasevic et al. 1996; Novak and Watts 1996; Sabik and Jeannot 1998; Trevisan et al. 1993), or GC coupled with a mass spectrometer (MS) detector (Albanis et al. 1998; Benfenati et al. 1990; de Almeida Azevedo et al. 2000; Hernandez et al. 2000; McLaughlin and Johnson 1997; Sabik and Jeannot 1998). Some GC methods have been refined into standard EPA methods for analysis of atrazine in drinking water and waste water. For GC-MS detection of atrazine, EPA methods 508.1 and 525.2 can be used. For detection of atrazine by GC-ECD, EPA methods 505 and 551.1 can be used, and for detection by GC-NPD, EPA methods 507 and 8141A can be used (IARC 1999).

HPLC methods generally use reverse-phase columns such as C-8, C-18, or octadecylsilane (ODS)-columns, and the sample constituents are resolved in different solvent systems. These have included acetonitrile/water gradients (Dankwardt et al. 1995), methanol/ammonium acetate gradient (Marcé et al. 1995), ammonium acetate/water gradients (Abián et al. 1993), or water/methanol gradients (Hogenboom et al. 1997). Detection of atrazine is done using a UV detector (Dankwardt et al. 1995), a diode array (Marcé et al. 1995) or MS (Abián et al. 1993; de Almeida Azevedo et al. 2000; Marcé et al. 1995) detection. Immunogenic methods are usually based on ELISA using sheep-based antibodies to atrazine (Amistadi et al. 1997; Dankwardt et al. 1995; Turiel et al. 1999). Other immunogenic methods have been developed in which the antibody is bound to a “dipstick”, and this is used to evaluate concentrations of atrazine in water or liquid food samples (Wittmann et al. 1996), while other sampling approaches have used immuno-affinity systems to concentrate atrazine prior to analysis by GC (Dallüge et al. 1999).

Aqueous samples suspected of containing atrazine may be concentrated and/or partly purified using solid phase extraction (SPE) or other approaches. Different matrices can be used for these SPE extractions, including XAD-2 resin-based columns (Baun and Nyholm 1996), or C_8 or C_{18} extraction columns

(commercially available as “Sep Pak”, “Bakerbond-SPE”, “Bondpac”, “Carbopak”, or others) (Albanis et al. 1998; Ferrari et al. 1998; Gaynor et al. 1995; McLaughlin and Johnson 1997; Mojasevic et al. 1996; Novak and Watts 1996), or combined solid phase columns. In the latter case, one combined solid phase columns consisted of 66.6% C-18 silica-bonded phase and 33.3% phenyl silica-bonded phase (Benfenati et al. 1990). Subsequent analysis of atrazine-containing samples by GC-MS analysis permitted a detection limit of atrazine of 0.002 μg/g (2 parts per trillion). The use of XAD-2 resins (Baun and Nyholm 1996) has been applied to bioassay of atrazine and the SEP-PAK preconcentration has been used prior to GC analysis (Mojasevic et al. 1996; Novak and Watts 1996). The other methods that can be used to improve extraction of the atrazine include microwave assisted extractions (Bouaid et al. 2000) and supercritical fluid extraction of atrazine from foodstuffs (Pensabene et al. 2000). A summary of methods of analysis of atrazine in environmental samples is supplied in Table 7-2.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of atrazine 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 atrazine.

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. Atrazine can be detected in a number of human tissues including urine (MacIntosh et al. 1999), plasma (Trochimowicz et al. 2001), skin (Lioy et al. 2000), and saliva (Denovan et al. 2000). Detection limits are not uniformly characterized, but for urine, are likely to be 1 μg/L (McIntosh et al. 1999). There are needs for better and

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

Sample matrix	Preparation method	Analytical method	Sample detecton limit	Percent recovery	Reference
Water	Cleanup through immuno-affinity filter, desorbed by glycine buffer, dried, then dissolved in ethyl acetate	GC-NPD	1.5 ng/L (NPD)	88–96%	Dalluge et al. 1999
Water	Solid phase microextraction of samples prepared for method validation; samples desorbed from SPE material directly in the injection port of the GC by exposure for 5 minute at 240 °C	GC-NPD	7.4 ng/L	Not reported	Ferrari et al. 1998
Subsurface waters	SPE of water samples containing atrazine; analysis conducted by GC-NPD, GC-ECD, or GC-MS; 2-L volumes of water were filtered onto the SPE matrix; samples eluted using dichloromethane, then volumes reduced under a stream of nitrogen	GC-NPD GC-ECD GC-MS	2 ng/L	85–110% for spiked surrogates	Albanis et al. 1998.
Surface waters	1–20 L of river water extracted by liquid-liquid technique (dichloromethane-water) or by SPE; dichloromethane (pesticide containing fraction) was collected and evaporated to dryness and sample dissolved in ethyl acetate; SPE with carbon black (Carbopack B; 500–666 µm) was used as the SPE; samples eluted by ethyl acetate	GC-NPD HPLC	0.4 ng/L GC 0.6 ng/L (HPLC)	67–100%	Sabik and Jeannot 1998
Sediments, aquatic plants	Material ground in a Wiley-mill, extracted in ethyl acetate, then sonicated material treated again, and extracts combined, then concentrated under a stream of nitrogen; dried material was dissolved in hexane	GC-ECD	Not reported	90%	Bennett et al. 2000

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

Sample matrix	Preparation method	Analytical method	Sample detecton limit	Percent recovery	Reference
Water and soil	Leachates of water and soil used to compare GC to ELISA approaches to atrazine detection; SPE used to concentrate samples prior to GC analysis; the RaPID assay ELISA kit was used (Strategic Diagnostics, Newark, Delaware)	GC-NPD ELISA	Water: 100 ng/L GC 50 ng/L ELISA Soil: 1.0 µg/kg GC 200 ng/kg ELISA	Not reported	Amistadi et al. 1997
Water and soil	Solid Phase Microextraction of pesticides from water sample; samples extracted from soil using microwave assisted extraction into methanol	GC-MS	Water: 40 ng/L Soil: <3 µg/kg	Soil: >80%	Hernandez et al. 2000
Soil	EPA method 8081A tested on soil extracts using SPE extraction followed by hexane elution and GC analysis; discusses linearity of response and reproducibility	GC-ECD	Not reported	Not reported	Lopez-Avila et al. 1992
Water and soil	EPA approved method 4670 for drinking water; water sample is filtered and brought to neutral pH, followed by proprietary ELISA method	ELISA	0.1 µg/L	Not reported	SDI 1999
Household dust	Sample collected by two different types of samplers that mimic uptake of a chemical by a person's hand that is placed on dusty surfaces; samples washed from sampler by sonication in hexane, followed by GC	GC-ECD	0.21 ng/cm^2 EL 4.0 ng/cm^2 LWW	Not reported	Lioy et al. 2000
Water	AOAC method for analysis of pesticides in water, including dealkylated atrazine; sample is extracted in dichloro-methane, dried over anhydrous sodium sulfate, brought up in methanol and concentrated	HPLC-UV	5.0 µg/L	89.6%	AOAC 1993

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

Sample matrix	Preparation method	Analytical method	Sample detecton limit	Percent recovery	Reference
Air	NIOSH method 5602, air samples are collected in a filter/sorbent tube at a flow rate of 0.2–1 L/minute, for a total volume of 12–480 L; following collection, sample is derivitized with diazomethane-derivitizing agent, silicic acid is added, then the sample is filtered, and analyzed by GC-ECD	GC-ECD	0.2 µg/sample	Not specifically reported (all analytes tested ranged from 69 to 150%)	NIOSH 1998a
Hand contamination	Hand washed in 150 mL of isopropanol in a polyethylene bag for 30 seconds; solution transferred to a glass jar; 10 mL removed from jar, derivatized in diazomethane derivitizing agent, silicic acid is added, followed by sample filtration and analysis by GC-ECD	GC-ECD	0.01 µg/mL	87.1–103%	NIOSH 1998b

AOAC = Association of Official Analytical Chemists; ECD = electron capture detection; ELISA = enzyme-linked immunosorbent assay; EPA = Environmental Protection Agency; GC = gas chromatography; HPLC = high performance liquid chromatography; MS = mass spectrometry; NIOSH = National Institute for Occupational Safety Chromatography; NPD = nitrogen-phosphorus detector; SPE = solid phase extraction; UV = ultraviolet

more uniform extraction methods for background levels of atrazine in the general population. Based on the analysis of atrazine in the saliva of pesticide applicators, levels in saliva appear to be at background levels at approximately 0.9 μg/L when sampled from the workers 1 month prior to the spraying season (Denovan et al. 2000). However, it was not known whether these reflected levels of background atrazine concentrations or metabolism of fat-stored atrazine in this population of pesticide workers. Therefore, more measures of salivary atrazine levels from the general population, or other potentially-exposed populations would be warranted to acquire a better understanding of atrazine background levels and background exposure levels. Other methods that attain a lower detection limit from other biological samples (e.g., urine analysis, blood analysis) may provide more sensitivity.

No data were located concerning methods of biological markers of atrazine effects. Atrazine has little toxicological effect, and does not produce uniform cancer-related effects (see Chapter 3) in laboratory animals. Therefore, at this time, it is not expected that accurate biomarkers would be found for atrazine.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for detection of atrazine in water, soil, sediments, food, household dust, subsurface samples, and air are based on GC, ELISA, and HPLC. The media considered to be of most concern for human exposure are food, water, and soil. As shown in Table 7-2, the most sensitive methodologies appear to be the ELISA based approaches and the GC-ECD, with detection limits of 0.4 ng/L for GC-NPD (Sabik and Jeannot 1998) and 2 ng/L for GC-NPD, GC-ECD, and GC-MS (Albanis et al. 1998). The ELISA assays will likely provide a much less expensive approach to environmental atrazine concentration determinations, with sensitivities approaching the levels of GC.

7.3.2 Ongoing Studies

The information in Table 7-3 was found as a result of a search of Federal Research in Progress (FEDRIP 2002) and Current Research Information System (CRIS 2002). These studies are being conducted to provide better means for food and environmental sample analysis. Most of the studies listed are examining the use of SPE approaches for better environmental sample stabilization prior to analysis.

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

Investigator	Affiliation	Research description	Sponsor
Camper ND, Riley MB	Clemson University, Clemson, South Carolina	Evaluation of SPE approaches for improving extraction of and stabilization of pesticides from water samples. Sampling and approaches were tested, and stability of environmental samples was shown to be better when shipped in SPE matrices as compare to shipment of water samples. Should lead to better accuracy of determinations of pesticides in aquatic matrices.	Hatch award
Giesy J	CSREES, Michigan State University	Development of chemical fractionation techniques, instrumental analyses, and bioassays to screen for "estrogenic" compounds in animal tissues and human food stuffs. Development of the use of wildlife sentinels for the effects of these compounds. Monitor for ecological health effects. Exposure evaluations.	Hatch
Hatfield JL	CSREES, New Jersey	Develop new and improved methods to detect environmentally important compounds and assess agricultural impacts on water, soil, and air quality. Methods will be developed to extend analytical procedures from development to production scale application.	USDA
Leidy RB	North Carolina State University, Raleigh, North Carolina	Development of solid phase extraction approaches for collection and stabilization of pesticides from water samples. Research will try to demonstrate that the SPE disks improve stability of sample during transport (over shipment of water samples), and will result in less error between test labs.	Hatch
Leidy RB	North Carolina State University, Raleigh, North Carolina	Validate methods for analyses conducted with 3M Empore disc membranes for pesticides including atrazine.	Hatch
Montvaldo R et al.	University of Puerto Rico, Mayaguez, Puerto Rico	Evaluation of solid phase extraction approaches for sampling water for pesticides. Testing of sample showed excellent recoveries of test pesticides. Will lead to better analysis of pesticides in field samples by minimizing transportation and storage losses.	Hatch
Mueller TC	University of Tennessee, Knoxville, Tennessee	Evaluation of SPE approaches for stabilization of pesticides in water. Research demonstrated that the SPE approaches improved pesticide stability during transport.	Hatch

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

Investigator	Affiliation	Research description	Sponsor
Sadowsky MJ, Wackett LP	CSREES, Minnesota	Investigation of the genetic regulation of the atrazine degradation genes by soil factors, such as the presence of nitrate and ammonia and triazine herbicides, and use these genes to design biosensors that can be used to detect triazine compounds in soils and water.	NRI

Source: CRIS 2002; FEDRIP 2002

CSREES = Cooperative State Research, Education, and Extension Service; NRI = National Research Institute; SPE = solid phase extraction; USDA = U.S. Department of Agriculture

8. REGULATIONS AND ADVISORIES

International, national, and state regulations and advisories regarding atrazine in air, water, and other media are summarized in Table 8-1. These values have been established because of the potential for atrazine to cause adverse health effects in exposed people.

The EPA (IRIS 2002) has calculated a chronic oral Reference Dose (RfD) for atrazine of $3.5x10^{-2}$ mg/kg/day based on a NOAEL of 3.5 mg/kg/day for decreased body weight gain in rats exposed for their lifetimes to 70 ppm atrazine in the diet. The NOAEL of 3.5 mg/kg/day atrazine was divided by uncertainty factors of 10 for extrapolation from animals to humans and 10 for human variability in sensitivity. EPA has not derived a Reference Concentration (RfC) for chronic inhalation or done a carcinogenicity assessment for lifetime exposure.

No inhalation MRLs have been derived for atrazine due to lack of data. An MRL of 0.01 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to atrazine based on a NOAEL of 1 mg/kg/day for decreased body weight gain in pregnant rabbits exposed to atrazine on gestational days 7–19 (Infurna et al. 1988) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

An MRL of 0.003 mg/kg/day has been derived for intermediate-duration oral exposure (15–365 days) to atrazine based on a LOAEL from a 19-day study in which pigs that were administered 1 mg/kg/day atrazine in the diet had decreased levels of estradiol-17β (E_2), resulting in delayed onset of estrus (Gojmerac et al. 1999). The MRL of 0.003 mg/kg/day was calculated by dividing the LOAEL of 1 mg/kg/day by an uncertainty factor of 300 (10 to account for the use of a LOAEL for delayed onset of estrus, 10 for extrapolation from animals to humans, and 3 for human variability). An uncertainty factor of 3 for human variability was used instead of 10 because the critical effect was identified in a sensitive population (young, developing female pigs). The existing database on the chronic-duration oral toxicity of atrazine was considered inadequate for MRL derivation.

Table 8-1. Regulations and Guidelines Applicable to Atrazine

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 3[a]	IARC 2001
WHO	Drinking water guideline	2 µg/L	WHO 2001
NATIONAL			
Regulations and Guidelines:			
a. Air:			
ACGIH	TLV–TWA	5 mg/m^3	ACGIH 2000
NIOSH	REL (TWA)	5 mg/m^3	NIOSH 2001
OSHA	PEL (8-hour TWA)	5 mg/m^3	OSHA 2001
b. Water			
EPA	Drinking water standards	3 µg/L	EPA 2001e 40CFR141.32 (e)(28)
	Drinking water standards		EPA 2002b
	DWEL	1.0 mg/L	
	MCLG	3 µg/L	EPA 2001d 40CFR141.50
	MCL	3 µg/L	EPA 2001c 40CFR141.61
c. Food			
EPA	Tolerances for residues (ppm)		EPA 2001h 40CFR180.220
	Cattle–fat, meat byproducts, and meat	0.02	
	Corn, fodder–field, pop, and sweet	15.0	
	Corn, forage–field, pop, and sweet	15.0	
	Corn–fresh and grain	0.25	
	Eggs	0.02	
	Goats–fat, meat byproducts, and meat	0.02	
	Guava	0.05	
	Hogs–fat, meat byproducts, and meat	0.02	
	Horses–fat, meat byproducts, and meat	0.02	
	Macadamia nuts	0.25	
	Milk	0.02	
	Poultry–fat, meat byproducts, and meat	0.02	
	Rye grass, perennial	15.0	
	Sheep–fat, meat byproducts, and meat	0.02	
	Sorghum-fodder and forage	15.0	
	Sorghum-grain	0.25	

Table 8-1. Regulations and Guidelines Applicable to Atrazine

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Tolerances for residues (ppm)		EPA 2001h
	Sugarcane–fodder and forage	0.25	40CFR180.220
	Wheat–fodder and straw	5.0	
	Wheat, grain	0.25	
	Tolerances for combined residues of atrazine and its metabolites (ppm)		
	Grass, range	4.0	
FDA	Bottled water	3 µg/L	FDA 2000b 21CFR165.110
	Food additives permitted for direct addition to food for human consumption—diethanolamide condensate based on a mixture of saturated and unsaturated soybean oil fatty acids (or stripped coconut fatty acids) as a surfactant in emulsifier blends	Added to the herbicide atrazine for application to corn	FDA 2000a 21CFR172.710
d. Other			
ACGIH	Carcinogenicity classification	A4[b]	ACGIH 2000
	RfD	3.5×10^{-2} mg/kg/day	IRIS 2001
	Effluent limitations for BOD5 and TSS		EPA 2001g 40CFR455.20
EPA	Toxic chemical release reporting; Community Right-to-Know; effective date of reporting	01/01/95	EPA 2001i 40CFR372.65
	Standards for hazardous waste TSD facilities—Henry's law constant less than 0.1 atm m^3/mol		EPA 2001b 40CFR265 Appendix VI
NRC	Acceptable daily intakes	2.15×10^{-2} mg/kg/day	HSDB 2001
STATE			
a. Air			
Alaska	Air contaminant standard	5 mg/m^3	BNA 2001
Connecticut	HAP		BNA 2001
	8 Hours	100 µg/m^3	
	30 Minutes	500 µg/m^3	
Hawaii	Air contaminant	5 mg/m^3	BNA 2001
Kentucky	Air quality		BNA 2001
	TAL (8 hours)	20 mg/m^3	
	Significant levels	1.276×10^{-3} pounds/hour	
Louisiana	Hazardous waste; air emission standards—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Atrazine

Agency	Description	Information	Reference
STATE *(cont.)*			
Michigan	PEL (TWA)	5 mg/m^3	BNA 2001
Nebraska	Hazardous waste; organic air emission standards for tanks and containers—compounds with Henry's law constant less than 0.1 atm m^3/mol		BNA 2001
New Hampshire	Toxic air pollutant		BNA 2001
	OEL	5 mg/m^3	
	24-Hour AAL	18 µg/m^3	
	Annual AAL	12 µg/m^3	
	24-Hour de minimus	1.67x10^{-3} pounds/hour	
	Annual de minimus	3.91x10^{1} pounds/year	
New Mexico	Toxic air pollutant		BNA 2001
	OEL	5 mg/m^3	
	Emissions	0.333 pounds/hour	
New York	PEL (TWA)	5 mg/m^3	BNA 2001
North Carolina	PEL (TWA)	5 mg/m^3	BNA 2001
Washington	PEL (TWA)	5 mg/m^3	BNA 2001
	Toxic air pollutants		BNA 2001
	ASIL (24-hour average)	17 µg/m^3	
Wisconsin	Emission rate with emission point <25 feet	4.176x10^{-1} pounds/hour	BNA 2001
	Emission rate with emission point >25 feet	1.752 pounds/hour	
b. Water			
Alabama	MCL	3 µg/L	BNA 2001
Alaska	MCL	3 µg/L	BNA 2001
Arizona	Drinking water guideline	3 µg/L	HSDB 2001
	Groundwater protection list		BNA 2001
	Safe drinking water—reporting limit	0.1 µg/L	BNA 2001
California	Drinking water standard	3 µg/L	HSDB 2001
	Pesticide contamination prevention—groundwater protection list		BNA 2001
Colorado	Groundwater quality standards	3 µg/L	BNA 2001
	MCL	3 µg/L	BNA 2001
Connecticut	Standards for quality of public drinking water—MCL	3 µg/L	BNA 2001
Delaware	MCL	3 µg/L	BNA 2001
Florida	Contaminant cleanup target level		BNA 2001
	Freshwater surface water criteria	1.8 µg/L (human health)	
	Marine surface water criteria	1.8 µg/L (human health)	
Georgia	MCL for drinking water	3 µg/L	BNA 2001
Hawaii	MCL	3 µg/L	BNA 2001
Idaho	Groundwater quality standards	3 µg/L	BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Atrazine

Agency	Description	Information	Reference
STATE *(cont.)*			
Illinois	MCL	3 µg/L	BNA 2001
Kansas	Surface water quality criteria		BNA 2001
	Aquatic life		
	Acute	170 µg/L	
	Chronic	3 µg/L	
	Domestic water supply	3 µg/L	
Kentucky	MCL	3 µg/L	BNA 2001
Maine	Drinking water guideline	3 µg/L	HSDB 2001
	Private water systems		BNA 2001
	Maximum exposure guideline	4.3×10^{-2} mg/L	
	Action level	2.1×10^{-2} mg/L	
Maryland	Drinking water	3 µg/L	BNA 2001
Michigan	MCL	3 µg/L	BNA 2001
	Effective date	07/30/92	
Minnesota	Drinking water guideline	20 µg/L	HSDB 2001
Mississippi	Groundwater standards	3 µg/L	BNA 2001
Missouri	MCL	3 µg/L	BNA 2001
Nebraska	Aquatic criteria[d]		BNA 2001
	Acute	330 µg/L	
	Chronic	12 µg/L	
	MCL	3 µg/L	BNA 2001
New Jersey	Groundwater quality criteria	3 µg/L	BNA 2001
	PQL	1 µg/L	
New Mexico	MCL	3 µg/L	BNA 2001
New York	Groundwater effluent limitations—maximum allowable concentration	7.5 µg/L	BNA 2001
	MCL	3 µg/L	BNA 2001
North Dakota	MCL	3 µg/L	BNA 2001
Ohio	MCL	3 µg/L	BNA 2001
Oklahoma	MCL	3 µg/L	BNA 2001
Rhode Island	Groundwater quality standard	3 µg/L	BNA 2001
	Preventive action limit	1.5 µg/L	
Rhode Island	MCLG	3 µg/L	BNA 2001
	MCL	3 µg/L	
South Carolina	MCL	3 µg/L	BNA 2001
South Dakota	Groundwater quality standards	3 µg/L	BNA 2001
Tennessee	MCL	3 µg/L	BNA 2001
Texas	MCL	3 µg/L	BNA 2001
Utah	Groundwater quality standards	3 µg/L	BNA 2001
	MCL	3 µg/L	BNA 2001
Vermont	Groundwater quality standards		BNA 2001
	Enforcement standard	3 µg/L	
	Preventive action level	1.5 µg/L	
	MCL	3 µg/L	BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Atrazine

Agency	Description	Information	Reference
STATE *(cont.)*			
Virginia	MCLG MCL	3 µg/L 3 µg/L	BNA 2001
Washington	MCLG MCL	3 µg/L 3 µg/L	BNA 2001
West Virginia	Groundwater standards	Not to exceed 3 µg/L	BNA 2001
Wisconsin	Groundwater quality standards (total chlorinated residues) Enforcement standard[e] Preventive action limit[e]	 3 µg/L 0.3 µg/L	BNA 2001
	MCLG[f] MCL	3 µg/L 3 µg/L	BNA 2001
Wyoming	Groundwater standards—MCL	3 µg/L	BNA 2001
c. Food		No data	
d. Other			
Arizona	Soil remediation levels Residential Non-residential	 20.0 mg/kg 86.0 mg/kg	BNA 2001
Arkansas	Hazardous waste management—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		BNA 2001
California	Hazardous substance list		BNA 2001
California	Pesticide registration—active ingredient that have the most significant data gaps, widespread use, and suspected to be hazardous to people		BNA 2001
	Restricted pesticide —agricultural, outdoor institutional, and outdoor industrial uses of pesticides containing atrazine are prohibited in the Pesticide Management Zones		BNA 2001
Colorado	Hazardous waste—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		BNA 2001
Delaware	Hazardous waste—compounds with Henry's law constant less than 0.1 atm m^3/mol		BNA 2001
Florida	Toxic substances in the workplace—substance list		BNA 2001
Iowa	Restrictions on distribution and use of pesticides		BNA 2001
Massachusetts	Containers adequately labeled pursuant to federal law		BNA 2001
	Oil and hazardous material list		BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Atrazine

Agency	Description	Information	Reference
STATE *(cont.)*			
Minnesota	Hazardous substance		BNA 2001
	RfD	$3.5x10^{-2}$ mg/kg/day	BNA 2001
	Health risk limit	20 µg/L	
	Toxic end point	Cardiovascular system	BNA 2001
New Jersey	Hazardous substance		BNA 2001
South Carolina	Hazardous waste—compounds with Henry's law constant less than 0.1 atm m^3/mol		BNA 2001
Tennessee	Hazardous substance site remediation goals	$3x10^{-3}$ ppm	BNA 2001
Washington	Pesticide regulation	Restricted use pesticide	BNA 2001
Wisconsin	Hazardous waste—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		BNA 2001
	Pesticide product restrictions		BNA 2001

[a]Group 3: not classifiable as to its carcinogenicity to humans
[b]A4: not classifiable as a human carcinogen
[c]Group C: possible human carcinogen
[d]Human health criteria at 10^{-5} risk level for carcinogens based on the consumption of fish and other aquatic organisms.
[e]Total chlorinated atrazine residues includes parent compound and the following metabolites of health concern: 2-chloro-4-amino-6 isopropylamino-s-triazine (formerly deethylatrazine), 2-chloro-4-amino-6-ethylamino-s-triazine (formerly deisopropylatrazine), and 2-chloro-4,6-diamino-s-triazine (formerly diaminoatrazine).
[f]Atrazine, total chlorinated residue includes atrazine and its metabolites, diaminoatrazine, diethylatrazine, and deisopropylatrazine.

ACGIH = American Conference of Governmental Industrial Hygienists; AAL = ambient air limits; ASIL = acceptable source impact levels; BOD = biological oxygen demand; BNA = Bureau of National Affairs; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HAL = health advisory level; HAP = hazardous air pollutant; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; OEL = occupational exposure limit; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation level; REL = recommended exposure limit; RfD = reference dose; TAL = threshold ambient limit; TLV = threshold limit values; TSD = treatment, storage, and disposal; TSS = total suspended solids; TWA = time-weighted average; WHO = World Health Organization

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10. GLOSSARY

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

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

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

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

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

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

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

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

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

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

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study which 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 which 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.

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.

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.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

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

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

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

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

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

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest 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) which 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 odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

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 science of quantitatively predicting 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 whereby 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 which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

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

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

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

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

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations 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.

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

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

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

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

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

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

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

Toxicokinetic—The study of 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 one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

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

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold 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 E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Atrazine
CAS Number: 1912-24-9
Date: September 2003
Profile Status: Draft 3 Post-Public
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 23
Species: Rabbit

Minimal Risk Level: 0.01 [X] mg/kg/day [ ] ppm

Reference: Infurna R, Levy B, Meng C, et al. 1988. Teratological evaluations of atrazine technical, atrazine herbicide, in rats and rabbits. J Toxicol Environ Health 24:307-319.

Experimental design: Groups of 19 female New Zealand White rabbits were artificially inseminated (gestation day 0) and administered 0, 1, 5, or 75 mg/kg/day atrazine (Aatrex) in 3% aqueous corn starch containing 0.5% Tween 80 by gavage on gestational days 7–19. Rabbits were observed twice daily for changes in appearance and behavior. Feed consumption and body weight changes were monitored throughout gestation. Dams were necropsied on gestational day 29. Ovaries were examined, corpora lutea were counted, uteri and contents were weighed, live fetuses and resorptions were counted, and liver weights were recorded. Fetuses were weighed, sexed, and examined for external, visceral, skeletal, and soft tissue abnormalities.

Effects noted in study and corresponding doses: Clinical signs related to treatment were increased incidence of stool variations (little, no, or soft stool) and bloody vulva. Absolute, but not relative, liver weight was decreased in the 75 mg/kg/day group. Food consumption and body weight gain were severely reduced during the treatment period in the high dose group, but rebounded after cessation of treatment; however, overall body weight gain corrected for weight of the uterus, placentas, and fetuses was significantly reduced. Slight, but statistically significant, reductions in food consumption and body weight gain were noted in the 5 mg/kg/day group.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL 1 mg/kg/day in pregnant rabbits, decreased body weight gain at ≥5 mg/kg/day

Uncertainty Factors used in MRL derivation:

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

Was a conversion used from ppm in food or water to a mg/body weight dose? If so, explain: None needed.

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: The MRL is supported by a number of studies showing decreased body weight gain in rats (Cantemir et al. 1997; Cooper et al. 1996b, 2000; Cummings et al. 2000b; Dési 1983; Eldridge et al. 1994a, 1999a; EPA 1984f, 1987d, 1987e; Infurna et al. 1988; Kniewald et al. 2000; Pinter et al. 1990; Santa Maria et al. 1987; Šimić et al. 1994; Suschetet et al. 1974; Tennant et al. 1994b; Ugazio et al. 1991a; Vos et al. 1983; Wetzel et al. 1994) and dogs (EPA 1987f). Other effects noted in rabbits in the Infurna et al. (1988) study occurred only in the high-dose group (75 mg/kg/day) and included increased incidence of stool variations (little, no, or soft stool), bloody vulva, absolute, but not relative, liver weight decrease, and severely reduced food consumption and body weight gain. Slight, but statistically significant, decreases in body weight gain occurred in the 5 mg/kg/day group. Other NOAELs and LOAELs for acute-duration exposures include: a NOAEL of 12.5 mg/kg/day for increased inflammation of the lateral prostate in adult male offspring of atrazine-treated rat dams (Stoker et al. 1999); a NOAEL of 5 mg/kg/day for increased resorptions/litter and decreased live fetuses/litter in rabbits exposed on gestational days 7–19 (Infurna et al. 1988); and a NOAEL of 1 mg/kg/day for developmental effects (decreased fetal body weight; increased incidence of nonossification of foot bones and patellae) in offspring of treated rabbit dams (Infurna et al. 1988); and a NOAEL of 10 mg/kg/day for developmental effects (incomplete ossification of skull, hyoid bone, teeth, forepaw metacarpals, and hindpaw distal phalanges) in rat offspring of dams exposed to 70 mg/kg/day (Infurna et al. 1988). The developmental effects were attributed to severe maternal toxicity related to severe decreases in food intake and body weight. Changes in serum and pituitary hormone levels have been seen at exposures of $\geq$50 mg/kg/day (Cooper et al. 2000; Stoker et al. 1999).

Agency Contact (Chemical Manager): Alfred S. Dorsey Jr., DVM

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Atrazine
CAS Number: 1912-24-9
Date: September 2003
Profile Status: Draft 3 Post-Public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 74
Species: Pig

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

Reference: Gojmerac T, Uremovic M, Uremovic S, et al. 1999. Reproduction disturbance caused by an s-triazine herbicide in pigs. Acta Veterinaria Hungarica 47(1):129-135.

Experimental design: Groups of nine female Swedish Landrace/Large Yorkshire cross pigs (6–7-month-old gilts) were administered 0 or 1 mg/kg/day atrazine in the feed for 19 days beginning with the onset of estrus (day 0). Blood samples were drawn 3 times daily at 3-hour intervals on the 5 days immediately following the final day of atrazine administration (this corresponded to the expected day of the next estrus [day 0] and 2 days before [days -1 and -2] and 2 days [days 1 and 2] after the expected estrus). Serum 17β-estradiol (E_2) concentrations in the blood samples were determined. Histopathological examination of the uterus was performed.

Effects noted in study and corresponding doses: E_2 concentrations were statistically significantly different ($p<0.001$) from controls on all 5 days measured. In controls, E_2 concentrations were high on days -2 and -1, then dropped on day 0 (beginning of estrus) and remained low on days 1 and 2. In treated animals, E_2 concentrations were lower than controls on days -2 and -1, and higher than controls on days 0 through 2. Treated pigs failed to exhibit overt signs of estrus onset and uterine histopathology indicated a state of uterine rest (diestrus) at the end of the observation period. A slight, but steady increase of E_2 hormone level was seen in the treated animals on day 24 of the estrus cycle (day 2). The study authors suggested that the balance of the E_2 hormone level was being gradually restored, which is the pattern that would be anticipated if the animals were about to go into estrus.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL 1 mg/kg/day in pigs, delayed onset of estrus

Uncertainty Factors used in MRL derivation:

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

An uncertainty factor of 3 for human variability was used instead of 10 because the critical effect was identified in a sensitive population (young, developing female pigs).

Was a conversion used from ppm in food or water to a mg/body weight dose? If so, explain: 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: Other systemic and reproductive effects have been observed in animals exposed to atrazine for 15–365 days. Decreased body weight gain was seen in rats at LOAELs of 2.7 mg/kg/day and above (Cantemir et al. 1997; Cooper et al. 1996b, 2000; Dési 1983; Eldridge et al. 1994a, 1999a; Kniewald et al. 2000; Laws et al. 2000; Suschetet et al. 1974; Trentacoste et al. 2001; Wetzel et al. 1994). Endocrine gland weights and serum and pituitary gland hormone levels were altered in rats at LOAELs as low as 6.9 mg/kg/day for 1 month (Cooper et al. 1996b, 2000; Eldridge et al. 1994a; Friedmann 2002; Laws et al. 2000; Trentacoste et al. 2001; Wetzel et al. 1994). Disrupted estrus cyclicity was seen in rats at the lowest LOAEL of 6.9 mg/kg/day (Wetzel et al. 1994). Other NOAELs and LOAELs observed included: a LOAEL of 50 mg/kg/day (NOAEL of 5 mg/kg/day) for increased relative liver weights in Sprague-Dawley and Donryu rats (Aso et al. 2000); a LOAEL of 2 mg/kg/day for degeneration of a small number of myocardial fibers, mild degeneration and inflammation and mild chronic interstitial hepatitis and subacute glomerulitis, degeneration and desquamation of proximal tubules, a 350% increase in serum gamma-glutamyl-transferase, and mild liver histological changes in pigs (Ćurić et al. 1999; Gojmerac et al. 1995); a LOAEL of 33 mg/kg/day (NOAEL of 4.6 mg/kg/day) for abnormal estrus cycle in Sprague-Dawley rats (Eldridge et al. 1999a); and a LOAEL of 2 mg/kg/day for ovarian histopathology, disrupted estrogen and progesterone levels, and delayed onset of estrus (Gojmerac et al. 1996), and ovarian cysts and disruption of estrus cyclicity (Ćurić et al. 1999).

Agency Contact (Chemical Manager): Alfred S. Dorsey Jr., DVM

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 they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, 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. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. 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, we have derived minimal risk levels (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.

They 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 the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

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 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 LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) 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, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. 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 No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (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 LSE Table 3-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 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 2 "18r" data points in 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 regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 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, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest 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 Cancer Effect Level (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 the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

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 intermediate and chronic 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 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level 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)		Reference
					Less serious (ppm)	Serious (ppm)	
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
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

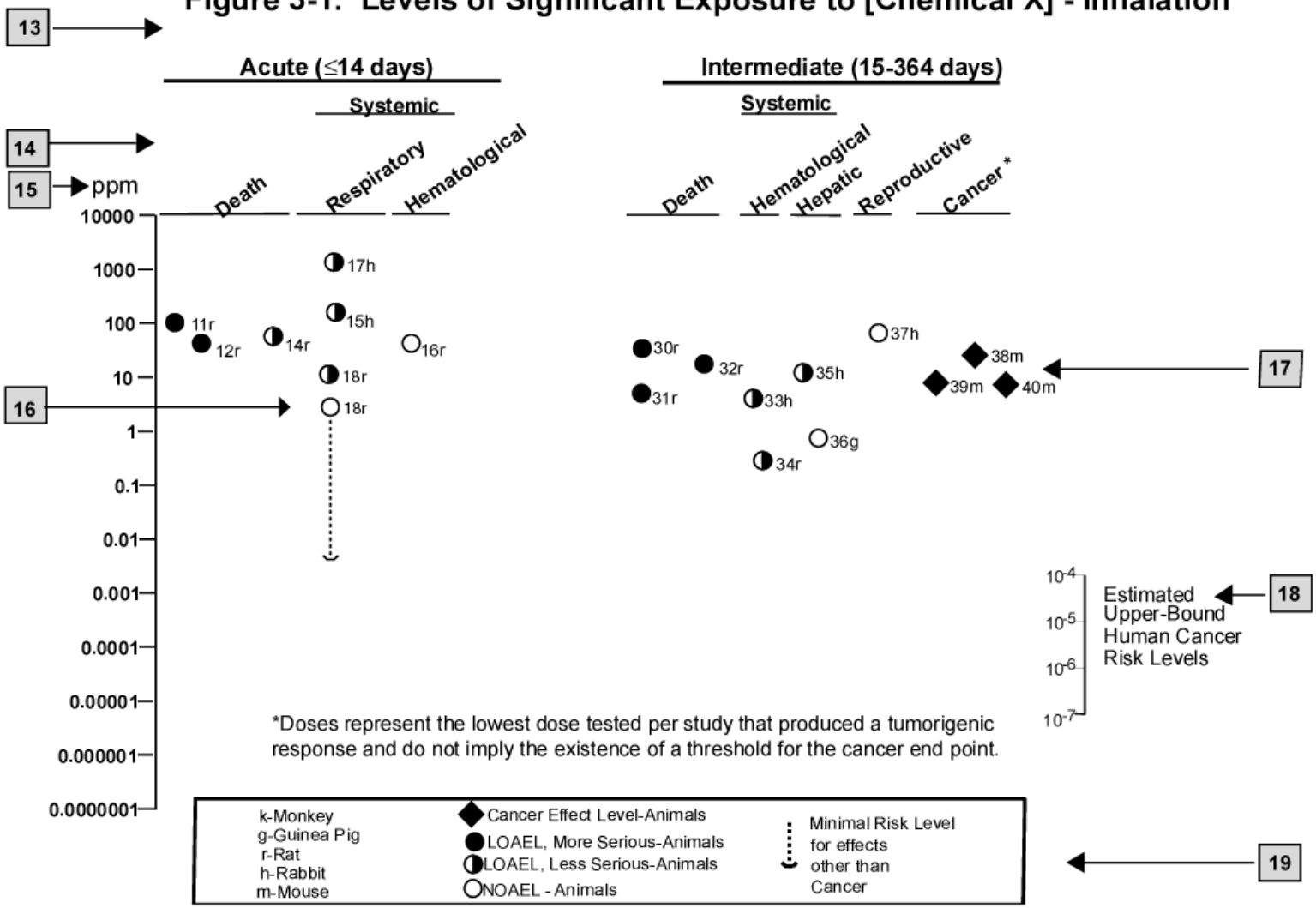
12 →

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

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

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



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
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
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotranferase
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
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
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	luteinizing hormone
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
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
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
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
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
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
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
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
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