TOXICOLOGICAL PROFILE FOR DIAZINON

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

September 2008

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 Diazinon, Draft for Public Comment was released in September 2006. This edition supersedes any previously released draft or final profile.

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE
Mailstop F-32
Atlanta, Georgia 30333

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for 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

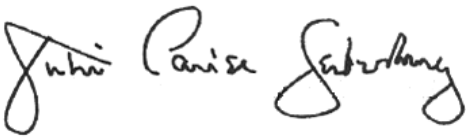
(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

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.

Howard Frumkin M.D., Dr.P.H.
Director
National Center for Environmental Health/
Agency for Toxic Substances and
Disease Registry



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 December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999(64 FR 56792); October 25, 2001 (66 FR 54014) and November 7, 2003 (68 FR 63098). 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: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

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

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

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

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

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

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

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

Referrals

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

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

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

G. Daniel Todd, Ph.D.
Carolyn Harper, Ph.D.
Paula Burgess, M.D.
ATSDR, Division of Toxicology and Environmental Medicine, Atlanta, GA

David Wohlers, Ph.D.
Michael H. Lumpkin, Ph.D.
Christina Coley, B.S.
Courtney M. Hard, B.S.
Syracuse Research Corporation, North Syracuse, NY

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

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

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PEER REVIEW

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

1. Douglas Crawford-Brown, Ph.D., Professor, Department of Environmental Sciences and Engineering, School of Public Health, University of North Carolina, Chapel Hill, North Carolina 27599,

2. Bhupendra Kaphalia, Ph.D., Associate Professor, Department of Pathology, University of Texas Medical Branch, Galveston, Texas 77555, and

3. Jim Riviere, D.V.M, Ph.D., Director, Center for Chemical Toxicology Research and Pharmacokinetics, Burroughs Wellcome Fund Distinguished Professor of Pharmacology, North Carolina State University, College of Veterinary Medicine, Raleigh, North Carolina 27606.

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

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

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

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1. PUBLIC HEALTH STATEMENT

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

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Diazinon has been found in at least 25 of the 1,699 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which diazinon is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may be harmful.

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

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

1.1 WHAT IS DIAZINON?

Description	Diazinon does not occur naturally in the environment. The pure chemical is an oil that is colorless and practically odorless. Commercial diazinon is a pale to dark brown liquid.
Uses • **Pesticide uses**	Diazinon is the common name of an organophosphorus insecticide used to control pest insects in soil, on ornamental plants, and on fruit and vegetable field crops. Diazinon is sold under common trade names including Alfatox, Basudin, AG 500, Dazzel, Gardentox, and Knoxout.

For more information on the physical and chemical properties of diazinon, and its production, disposal and use, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO DIAZINON WHEN IT ENTERS THE ENVIRONMENT?

Sources	Diazinon may enter the environment from agricultural and household application of the chemical to control insects. After diazinon has been applied, it may be present in the soil, surface waters (such as rivers and ponds), and on the surface of plants.
How diazinon breaks down	
• Air	Diazinon is rapidly broken down to a number of different compounds.
• Water and soil	Diazinon is quickly broken down in a few hours to 2 weeks.
• Plants and animals	Diazinon is rapidly broken down by most animals that eat it and is not likely to build up to high or dangerous levels in animals or plants that you might eat.

For more information on diazinon in the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO DIAZINON?

Food-primary source of exposure	Small amounts of diazinon have been detected in foods sold to consumers, but studies by the U.S. Food and Drug Administration (FDA) have found that the levels in food are far below the level that might cause any harmful health effects.
Air	You may be exposed to diazinon in air in agricultural areas where diazinon is extensively used or in urban areas where it is applied to lawns and gardens.
Drinking water	You may be exposed to diazinon by drinking contaminated water.
Recently sprayed plants	You may be exposed to diazinon by touching diazinon-treated plant materials such as grass clippings.
Workplace	People who work in the manufacture and professional application of diazinon have the most significant exposure to this insecticide.

Consumer products	Although diazinon was formerly used as the active ingredient in home and garden pest control products, sale of these home and garden products in the United States was stopped in 2004. However, previously purchased diazinon-containing home and garden products may still be in use and present the potential for exposure.

For more information on human exposure to diazinon, see Chapter 6.

1.4 HOW CAN DIAZINON ENTER AND LEAVE MY BODY?

Enter your body	
• **Inhalation**	If you breathe air containing diazinon, you may absorb it into your body through your lungs.
• **Ingestion**	Diazinon in food or water may also rapidly enter your body through the digestive tract.
• **Dermal contact**	Diazinon may enter your body across the skin.
Leave your body	Once in the body, diazinon is rapidly broken down and eliminated from the body mainly in the urine. Diazinon has not been shown to accumulate in any tissues and most of the chemical is eliminated from the body within 12 days.

For more information on how diazinon enters and leaves the body, see Chapter 3.

1.5 HOW CAN DIAZINON AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in animal and human studies.

Human exposure **• High exposure**	Short exposures to high levels of diazinon can affect the nervous system. Symptoms include: • headache, dizziness, weakness • feelings of anxiety • constriction of the pupils of the eye • not being able to see clearly
• Very high exposure	Exposures to very high levels can cause more severe symptoms including: • nausea, vomiting, abdominal cramps, and diarrhea • slow pulse • pinpoint pupils • difficulty breathing • passing out (coma) Signs or symptoms of nervous system damage may occur within 30–60 minutes. If you experience these symptoms, you should seek medical attention immediately. Emergency rooms have drugs that stop the harmful effects of diazinon.
Long-term exposure to low levels	There is no evidence that long-term exposure to low levels of diazinon causes any harmful health effects in people.
Cancer	Diazinon has not been shown to cause cancer in people or animals. The International Agency for Research on Cancer (IARC) has not classified diazinon for carcinogenicity. EPA classified diazinon as a Group E chemical (evidence of noncarcinogenicity for humans).

Further information on the health effects of diazinon in humans and animals can be found in Chapters 2 and 3.

1.6 HOW CAN DIAZINON AFFECT CHILDREN?

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

Effects in children	It is likely that children would have the same health effects as adults. We do not know whether children would be more sensitive than adults to the effects of diazinon. One study found neurological and bone effects in young children living in a house were diazinon was misused to control a flea infestation.
Birth defects	There is no evidence that environmental exposure to diazinon causes birth defects or other developmental effects in people. In animals, levels of exposure to diazinon high enough to affect the health of pregnant mothers caused developmental effects in their newborn babies.
Breast milk	Animal studies have shown that diazinon and/or its breakdown products can be transferred from a pregnant mother to a developing fetus, but no human data were located regarding the transfer of diazinon from the mother to the fetus or nursing infant.

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

Cautions for those who live in agricultural areas	People who live near agricultural areas where diazinon is still used should stay away from the area that has been treated. Diazinon can be dispersed some distance from a spray zone by air currents and runoff water. If you are aware that diazinon is being sprayed in the vicinity, you may want to go indoors or leave the area for a short time. Agricultural workers who have come into contact with relatively large amounts of diazinon at work may need to remove and wash contaminated clothing before coming into contact with other family members.
Wash fruits and vegetables	To reduce the risk of exposure to diazinon residue on fresh fruits or vegetables, wash the foods prior to eating them.
Properly use insect sprays	Occasionally, diazinon may be improperly sprayed inside the home to kill insects. Make sure that any person who treats your home with pesticides is properly certified. Ask what chemical or chemicals are being used. Diazinon is a “restricted use” chemical and is no longer registered for residential indoor or garden use.

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

Measuring effects	Most of the signs and symptoms resulting from diazinon poisoning are due to the inhibition of an enzyme called acetylcholinesterase in the nervous system. This enzyme is also found in your red blood cells and a similar enzyme (plasma cholinesterase) is found in blood plasma. The most common test for exposure to many organophosphorus insecticides, including diazinon, is to determine the level of cholinesterase activity in the red blood cells or plasma. It takes time for this enzyme to completely recover to normal levels following exposure. Therefore, a valid test may be conducted a number of days following the suspected exposure. This test indicates only exposure to an insecticide of this type. It does not specifically show exposure to diazinon.
Detecting exposure	Specific tests are available to determine the presence of diazinon or its breakdown products in blood, body tissue, and urine. These tests are only useful if done within a few hours or days of exposure. This is because diazinon is rapidly broken down and excreted from the body.

Information about tests for detecting diazinon in the body is given in Chapters 3 and 7.

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

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

Regulations and recommendations can be expressed as “not-to-exceed” levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

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

Some regulations and recommendations for diazinon include the following:

Drinking water	The EPA has determined that exposure to diazinon in drinking water at a concentration of 20 micrograms per liter (µg/L) for up to 10 days is not expected to cause any harmful effects in a child. The EPA has determined that lifetime exposure to 1 µg/L diazinon in drinking water is not expected to cause any harmful effects.
Food	The EPA has also set tolerances for residues of diazinon in various raw food products of 0.1–40 parts of diazinon per million parts of food (ppm).

For more information on regulations and advisories, 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 that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

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

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

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

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO DIAZINON IN THE UNITED STATES

Diazinon is an organophosphorus insecticide primarily used for agricultural purposes and is released to the environment through spraying on a wide variety of agricultural crops and at agricultural sites. Once diazinon is introduced into the environment, it may be activated by atmospheric photooxidation or degraded by hydrolysis or biodegradation mediated by microorganisms found in most sediment, soils, and water. Diazinon and diazoxon can be transported from the site of application by precipitation, fog, and wind to other areas. Since diazinon is moderately mobile in soils under certain conditions, it has the potential to migrate through the soil and into groundwater. Volatilization of diazinon from ground surfaces following aerial applications has been observed. Data from limited studies suggest that bioconcentration of diazinon does not occur to a significant extent in most aquatic organisms tested, and that it is rapidly metabolized when it is accumulated.

Significant exposure of the general population to diazinon is not likely at present, due to the ban on residential uses. Diazinon was formerly used in household and garden products for pest control. However, manufacturing of indoor use products was discontinued on June 30, 2001 and production of non-agricultural outdoor use products containing diazinon was discontinued on June 30, 2003. As of December 31, 2004, sales of diazinon-containing products for residential use were discontinued, although numerous restricted-use commercial products that contain diazinon are still available. Because diazinon-containing products are no longer sold for residential use, potential for significant exposure of the general population is expected to decrease as supplies that were obtained and stored before discontinuation are expended. General population exposure to diazinon may occur through ingestion of contaminated food or drinking water and inhalation. Ingestion of foods contaminated with small residues of diazinon is the most likely route of exposure for the general population not living in areas where diazinon is extensively used. The general population may also be exposed to diazinon through inhalation of contaminated ambient (outdoor) air.

Populations living within or very near areas of heavy agricultural diazinon use would have an increased risk of exposure to relatively larger amounts of diazinon through dermal contact with contaminated plants, soils, surface waters, or artificial surfaces such as playground equipment and pavements; by inhalation of the mist formed from the applied insecticide; or by ingestion of water or food-borne residues. Those likely to receive the highest levels of exposure are those who are involved in the

production, formulation, handling, and application of diazinon, farm workers who enter treated fields prior to the passage of the appropriate restricted entry intervals, and workers involved in the disposal of diazinon or diazinon-containing wastes. Dermal contact appears to be the major route of exposure for workers. Inhalation of diazinon in occupational settings depends on its volatility, the type of formulation used, and the application technique employed.

Children are expected to be exposed to diazinon by the same routes that affect adults. Small children are more likely to come into contact with diazinon residues that may be present in soil and dust, due to increased hand-to-mouth activity and playing habits. Diazinon has been detected in foods found in infant and toddler diets at concentrations of up to 0.46 mg/kg food. No data were located regarding diazinon in breast milk; therefore, an adequate determination of the importance of this route of child exposure has not been made.

See Chapter 6 for more detailed information regarding concentrations of diazinon in environmental media.

2.2 SUMMARY OF HEALTH EFFECTS

Diazinon is considered to be of moderate toxicity compared to other organophosphates. The principal toxic effect of diazinon in humans and laboratory animals is inhibition of acetylcholinesterase (AChE), which results in the accumulation of acetylcholine at acetylcholine receptors leading to cholinergic responses in the peripheral (muscarinic and nicotinic) and central nervous system and neuromuscular junctions.

High-level acute exposure to diazinon causes severe AChE inhibition that often leads to cholinergic signs and symptoms, manifest as reversible neuromuscular dysfunction when treated or when exposure is terminated. These manifestations include muscarinic effects (bronchoconstriction, increased bronchosecretion, nausea and vomiting, diarrhea, bradycardia, hypotension, miosis, urinary incontinence), nicotinic effects (tachycardia, hypertension, muscular twitching and weakness, fasciculation, cramping), and central nervous system effects (anxiety, apathy, depression, giddiness, drowsiness, insomnia, nightmares, headaches, confusion, ataxia, depressed reflex, seizure, respiratory depression, coma). In sufficiently high exposures (accidental or intentional), respiratory and cardiac failure and death may result without timely treatment intervention. The cholinergic manifestations of high acute exposure to diazinon have also been reported in animals and include anorexia, ataxia, epistaxis, tremors, listlessness, gasping,

convulsions, tachypnea, dyspnea, prostration, fasciculations, twitches, exophthalmos, diarrhea, salivation, diuresis, lacrimation, prostration, Straub tail reflex, and hypothermia. Clinical signs of diazinon neurotoxicity following repeated oral exposure in animals have been reported at doses ranging from 30 to 300 mg/kg/day. Limited information is available regarding clinical signs of neurotoxicity in animals exposed to diazinon by inhalation. One study reported decreased activity and salivation responses in rats exposed to an aerosol of diazinon for 4 hours at an exposure level of 2,330 mg/m^3.

As previously noted, the systemic toxicity of diazinon is mainly attributable to its action on the nervous system. Although AChE is intimately associated with neurotransmission within the central and peripheral nervous system, AChE is also found in erythrocytes (red blood cells [RBCs]). The blood plasma of humans and animals contains cholinesterases as well. Plasma cholinesterase (ChE) in humans is comprised almost entirely of butyrylcholinesterase (also known as pseudocholinesterase), whereas AChE constitutes a portion of the plasma ChE of animals, the relative amount of which is species dependent. In both humans and animals, measures of plasma ChE and RBC AChE activities have been used as indicators of exposure to cholinesterase inhibitors such as diazinon. Plasma ChE inhibition may often be observed at exposure levels lower than those inducing measurable RBC AChE inhibition. However, decreased activity of AChE is more indicative of a potential neurotoxic effect because RBC AChE is identical to neural AChE, whereas butyrylcholinesterase has not been demonstrated to play a role in the development or function of the central or peripheral nervous system.

Numerous animal studies and limited controlled human studies identify levels of exposure to diazinon resulting in plasma ChE, RBC AChE, and/or brain AChE inhibition. RBC and/or brain AChE inhibition of 20–59% is considered to represent a less serious adverse neurological effect in the absence of more serious indicators of neurotoxicity. In this Toxicological Profile, “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. The animal studies identified exposure levels at which diazinon caused RBC AChE inhibition in the absence of more serious indicators of neurotoxicity, which indicates that RBC AChE inhibition at such exposure levels may represent the most sensitive effect for diazinon toxicity. For example, inhibition of RBC and/or brain AChE at magnitudes ranging from 20 to 60% (in the absence of clinical signs) was observed following repeated oral dosing in the range of 0.3–75 mg/kg/day. In a repeated-exposure inhalation study, exposure to an airborne concentration of 1.57 mg/m^3, 6 hours/day, 5 days/week for 3 weeks resulted in 36–39% RBC AChE inhibition in rats.

Plasma ChE inhibition can typically be observed at doses lower than those required to produce significant RBC and/or brain AChE inhibition; RBC AChE appears to be more sensitive than brain AChE to diazinon toxicity. Following single oral dosing, peak cholinesterase inhibition is typically observed at 6–12 hours. Results of longer-term oral studies indicate that diazinon-induced plasma ChE and RBC AChE inhibition increases in severity with exposure duration to a peak at approximately 35 days; after which the severity of the inhibition remains relatively constant. Rat and dog studies indicate that females may be more sensitive than males to diazinon-induced cholinesterase inhibition, particularly with respect to brain AChE inhibition. Diazinon-induced neurohistopathological effects have not been demonstrated.

Diazinon does not appear to be a reproductive or developmental toxicant at exposure levels that do not result in maternal toxicity. There is limited evidence of morphological changes in spleen, thymus, and lymph nodes of animals following oral exposure to relatively high doses of diazinon, but no studies have demonstrated compromised immunological function. Predominantly negative results have been reported in testing of diazinon for genotoxicity. Two epidemiological studies reported weak associations between exposure to diazinon and lung cancer. Results of a few case-control studies have suggested possible links between diazinon exposure and non-Hodgkin's lymphoma, multiple myeloma, and childhood brain cancer. However, all of these studies involved exposure to other pesticides as well. A 2-year oral cancer bioassay in rats and mice did not find evidence for diazinon-induced carcinogenicity.

2.3 MINIMAL RISK LEVELS (MRLs)

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

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development

or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Diazinon is one member of a class of organophosphates that share a common mechanism of action, namely inhibition of AChE. Although the Toxicological Profile for Diazinon presents MRLs derived for diazinon in particular, human exposure scenarios may include simultaneous exposure to multiple organophosphate AChE inhibitors. MRLs derived specifically for diazinon may not be adequately protective for exposure scenarios that include exposure to multiple similarly-acting organophosphate AChE inhibitors.

Inhalation MRLs

An acute-duration inhalation MRL for diazinon was not derived due to the lack of suitable acute-duration human or animal data. Available reports of neurotoxicity indicators in humans exposed to diazinon by the inhalation route of exposure do not include quantitative data regarding exposure levels (Coye et al. 1987; Dahlgren et al. 2004; Kamha et al. 2005; Maizlish et al. 1987; Rayner et al. 1972; Richter et al. 1992; Soliman et al. 1982; Stalberg et al. 1978). Some of these exposures included multiple exposure routes and exposures to other pesticides as well. Available acute-duration inhalation data in animals are restricted to a single report of nasal discharge, polyuria, decreased activity, and salivation in a group of five rats exposed to a diazinon aerosol at a concentration of 2,330 mg/m^3. This study was not suitable for MRL derivation because it included a single exposure level at which serious effects were observed and no supporting data were available.

- An MRL of 0.01 mg/m^3 has been derived for intermediate-duration inhalation exposure (15–364 days) to diazinon.

This MRL is based on a no-observed-adverse-effect level (NOAEL) of 1.57 mg diazinon/m^3 for RBC AChE inhibition (a critical target of diazinon toxicity) observed in a 21-day study in hybrid rats (Hartman 1990).

No human reports were located regarding intermediate-duration inhalation exposure to diazinon. A single animal study (Hartman 1990) was located in which toxic effects of intermittent exposure to aerosols of diazinon for 21 days were assessed. This study served as the principal study for deriving an intermediate-duration inhalation MRL for diazinon. Support for the selection of diazinon-induced RBC AChE

inhibition as the critical effect is provided by the results of numerous animal studies that employed the oral exposure route. In the principal inhalation study (Hartman 1990), groups of rats (10/sex) were exposed to control air or air containing four different concentrations of aerosolized diazinon (0.05, 0.46, 1.57, or 11.6 mg/m^3) for 6 hours/day, 5 days/week for 3 weeks. No clinical signs of organophosphate neurotoxicity or effects on survival or body weight were observed. Histopathology of the nasal tract and lungs was normal in all groups; no histopathological effects were seen in spleen, heart, liver, kidney, and adrenal gland (examined only in the 11.6 mg/m^3 groups). Plasma ChE activity and RBC and brain AChE activity in the male and female rats are shown in Table 2-1. Significant reductions in plasma ChE (marker for exposure) were seen in males at exposure levels ≥1.57 mg/m^3 and in females at exposure levels ≥0.46 mg/m^3. Organophosphate-induced plasma ChE inhibition is typically observed at exposure levels lower than those inducing measurable RBC or brain AChE inhibition. Plasma ChE inhibition is used as an indicator of exposure, but does not serve as a reliable indicator of a neurotoxic effect. However, inhibition of RBC AChE and brain AChE represents a relevant neurological effect. In the principal study (Hartman 1990), significant reductions in RBC AChE activity (surrogate marker for neural AChE activity) were seen in male rats at 11.6 mg/m^3 and in female rats at 1.57 and 11.6 mg/m^3 (Table 2-1). Treatment-related 20–59% RBC or brain AChE inhibition is considered to represent a less serious adverse effect in the absence of more clear indicators of neurotoxicity (Chou and Williams-Johnson 1998). The 10% RBC AChE inhibition observed in the 1.57 mg/m^3 group of female rats is below the level of inhibition considered to represent an adverse effect. Therefore, the 1.57 mg/m^3 exposure level is a NOAEL and the highest exposure level (11.6 mg/m^3) is the lowest-observed-adverse-effect level (LOAEL) for 36 and 39% RBC AChE inhibition in the male and female rats, respectively. There was no significant difference between brain AChE activity in any of the exposure groups of male rats and that of vehicle controls. All diazinon-exposed groups of female rats exhibited significantly decreased brain AChE activity, relative to vehicle controls. The report of significantly increased brain AChE inhibition in the female rats of all exposure levels is indicative of an inherent problem with the brain data set, perhaps related to tissue collection or quantitative analysis of enzymatic activity in the brain tissue of the female rats. Furthermore, results of repeated oral dosing (Singh 1988) indicate that the male and female rats are comparably sensitive to diazinon-induced effects on both RBC and brain AChE activity. Therefore, the report (Hartman 1990) of significant brain AChE inhibition in the female rats exposed to diazinon by inhalation at levels much lower than the LOAEL of 11.6 mg/m^3 for RBC AChE inhibition is questionable, and a clear LOAEL for brain AChE inhibition cannot be determined.

Benchmark dose (BMD) analysis of the critical effect data sets for AChE inhibition from the principal study of Hartman (1990) was not possible. Although mean values for RBC and brain AChE activity were

Table 2-1. Effect of Aerosol Diazinon on Plasma ChE and RBC and Brain AChE Activity in Male and Female Rats Exposed for 6 Hours/Day, 5 Days/Week for 3 Weeks

	Mean plasma ChE activity in U/L (percent change from controls)	Mean RBC AChE activity in U/L (percent change from controls)	Mean brain AChE activity in U/g (percent change from controls)
Males			
Vehicle controls	368.9	894.2	3.893
0.05 mg/m^3	401.5 (+9%)[a]	908.6 (+2%)	3.855 (-1%)
0.46 mg/m^3	351.4 (-5%)	849.5 (-5%)	3.898 (0%)
1.57 mg/m^3	316.6 (-14%)[b]	840.1 (-6%)	3.737 (-4%)
11.6 mg/m^3	297.9 (-19%)[b]	573.0 (-36%)[a]	3.883 (0%)
Females			
Vehicle controls	631.8	887.7	3.742
0.05 mg/m^3	615.5 (-3%)	882.7 (-1%)	2.838 (-24%)[a]
0.46 mg/m^3	506.0 (-20%)[b]	943.0 (+6%)	3.106 (-17%)[b]
1.57 mg/m^3	459.0 (-27%)[a]	798.6 (-10%)[b]	2.983 (-20%)[b]
11.6 mg/m^3	361.0 (-43%)[a]	545.0 (-39%)[a]	2.369 (-37%)[a]

[a]statistically significantly different from control ($p \leq 0.01$)
[b]statistically significantly different from control ($p \leq 0.05$)

AChE = acetylcholinesterase; ChE = cholinesterase; RBC = red blood cell

Source: Hartman 1990

reported, measures of variance (standard deviation or standard error) were not included in the report. The NOAEL of 1.57 mg/m^3 for RBC AChE activity in the male and female rats of the principal study (Hartman 1990) served as the point of departure for deriving an intermediate-duration inhalation MRL for diazinon. The NOAEL was adjusted for intermittent exposure as follows:

$NOAEL_{ADJ}$ = 1.57 mg diazinon/m^3 x 6 hours/24 hours x 5 days/7 days = 0.28 mg diazinon/m^3

A regional deposited dose ratio ($RDDR_{ER}$) of 1.558 for extrarespiratory effects was used to extrapolate from rats to humans. The $RDDR_{ER}$ was calculated using the parameters listed in Table 2-2 and EPA's software (Version 2.3) (EPA 1994b) for calculating RDDRs.

The human equivalent concentration was calculated using Equation 4-5 (EPA 1994b) as follows:

$NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x $RDDR_{ER}$ = 0.28 mg diazinon/m^3 x 1.558 = 0.44 mg diazinon/m^3

The $NOAEL_{HEC}$ of 0.44 mg/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability) resulting in an intermediate-duration inhalation MRL of 0.01 mg/m^3.

No human or animal data were located regarding health effects from chronic-duration inhalation exposure to diazinon, precluding the derivation of a chronic-duration inhalation MRL for diazinon.

Oral MRLs

- An MRL of 0.006 mg/kg/day has been derived for acute-duration oral exposure (1–14 days) to diazinon.

The acute-duration oral MRL is based on a NOAEL of 0.6 mg/kg/day and a LOAEL of 1.2 mg/kg/day for >20% RBC AChE inhibition in rats exposed to diazinon in the diet (Davies and Holub 1980a).

Available information regarding health effects in humans following acute-duration oral exposure to diazinon is restricted to individual case reports of serious effects and death, which precludes derivation of an acute-duration oral MRL based on human data. Most acute-duration oral studies in animals involved diazinon doses that caused serious neurological effects. One single-dose oral gavage study (unpublished) identified a NOAEL of 2.5 mg/kg and a LOAEL of 25 mg/kg for 35% RBC AChE inhibition and 36%

Table 2-2. Parameters Used to Calculate the Regional Deposited Dose Ratio ($RDDR_{ER}$) for Diazinon-induced Extrarespiratory Effects Using EPA's Software (Version 2.3)

Biological parameters[a]	Rat	Human
Surface area		
Extrathoracic	15 cm^2	200 cm^2
Tracheobronchial	22.5 cm^2	3,200 cm^2
Pulmonary	0.34 m^2	54 m^2
Minute ventilation	147.24 mL	13.8 L
Body weight	196 g	70 kg

[a]Parameters are default values for rats and humans from the EPA software, except for the rat body weight, which was the mean body weight for the 1.57 mg/m^3 exposure group of female rats.

Mass Median Aerodynamic Diameter (MMAD) = 0.85 µm from lower limit of 0.8 µm and upper limit of 0.9 µm for the 1.57 mg/m^3 exposure group of female rats reported by Hartman (1990).

Geometric Standard Deviation (GSD) = 1.3 µm from lower limit of 1.2 µm and upper limit of 1.4 µm reported by Hartman (1990).

Source: Hartman 1990

brain AChE inhibition (EPA 2000a). However, the single-dose gavage level of 2.5 mg/kg was the lowest dose tested in a similar study (unpublished) and represented a LOAEL for 40% RBC AChE inhibition (EPA 2000a). In yet another unpublished study (EPA 1996), rats were administered diazinon in the diet for 28 days and assessed for cholinesterase inhibition at weeks 1, 2, and 4. An estimated dose of 2.4 mg/kg/day resulted in 38–59% RBC AChE inhibition, which was observed as early as week 1 and peaked at week 2. The next lower dose (0.02 mg/kg/day) represented a NOAEL.

Results of repeated-dose oral animal studies indicate that diazinon-induced AChE inhibition progressively increases in magnitude with time. For example, in female Wistar rats administered diazinon (99.2% purity) in the diet for 92 days, RBC AChE activity was significantly depressed as early as day 8 (Davies and Holub 1980a). By day 12, the magnitude of RBC AChE inhibition was approximately 5 and 22% at dietary concentrations resulting in doses of approximately 0.6 mg/kg/day (NOAEL) and 1.2 mg/kg/day (LOAEL), respectively. The study of Davies and Holub (1980a) identified the lowest LOAEL for the critical effect (22% RBC AChE inhibition) associated with the highest NOAEL for acute-duration oral exposure to diazinon and was therefore selected as the principal study for deriving an acute-duration oral MRL for diazinon.

In the principal study (Davies and Holub 1980a), female Wistar rats were administered diazinon (99.2% purity) in the diet at concentrations of 0, 5, 10, or 15 ppm for 92 days. Blood samples were collected on treatment days 3, 8, and 12 from 10 rats/group for assessment of plasma ChE and RBC AChE activity. Other groups of similarly-treated rats were sacrificed (n=6) for assessment of brain AChE activity. All rats were assessed daily for clinical signs of neurotoxicity and body weights and food intake were monitored throughout the treatment period. Based on reported food consumption and body weight data, calculated doses for the first 12 days of exposure were 0.6, 1.2, and 1.8 mg/kg/day for the 5- 10-, and 15-ppm exposure groups, respectively.

No clinical signs of toxicity were observed in any of the treated groups. At treatment day 12, treatment-related effects included 43, 70, and 73% plasma ChE inhibition and 5, 22, and 33% RBC AChE inhibition in the 0.6, 1.2, and 1.8 mg/kg/day dose groups, respectively. There was no significant effect on brain AChE activity. Plasma ChE inhibition is used as an indicator of exposure, but does not serve as a reliable indicator of a neurotoxic effect. Therefore, plasma ChE inhibition was not considered relevant to the selection of the critical effect for diazinon. However, inhibition of RBC AChE and brain AChE represents a relevant neurological effect. Treatment-related 20–59% RBC or brain AChE inhibition is considered to represent a less serious adverse effect in the absence of more clear indicators of

neurotoxicity (Chou and Williams-Johnson 1998). The principal study (Davies and Holub 1980a) identified a NOAEL of 0.6 mg/kg/day and a LOAEL of 1.2 mg/kg/day for 22% RBC AChE inhibition at interim day 12 assessment of female rats administered diazinon in the diet for 92 days.

BMD analysis of the critical effect data (RBC AChE inhibition) was not attempted because quantitative statistical data (mean and standard error or standard deviation) for the critical effect were presented only in graphical format (i.e., numerical values were not presented). The NOAEL of 0.6 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) resulting in an intermediate-duration inhalation MRL of 0.006 mg/kg/day.

- An MRL of 0.002 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to diazinon.

The intermediate-duration MRL is based on RBC AChE inhibition in female rats exposed to diazinon in the diet (Davies and Holub 1980a).

Available human information regarding intermediate-duration oral exposure to diazinon is restricted to a controlled study in which four male volunteers were administered diazinon in gelatin capsules at a dose level of 0.03 mg/kg/day for up to 31 days (EPA 2001). There were no treatment-related clinical signs. Approximately 22–42% plasma ChE inhibition was noted as early as treatment day 8 and reached a maximum of 47–55% by day 20 or the end of treatment. Because there was no indication of treatment-related effects on RBC AChE activity or clinical signs of neurotoxicity, the 0.03 mg/kg/day dose level represents a free-standing NOAEL.

Results of numerous oral studies in animals identify AChE inhibition as the most sensitive effect of diazinon toxicity following oral exposure. Table 2-3 presents a summary of NOAELs and LOAELs for RBC and brain AChE inhibition following intermediate-duration oral exposure to diazinon. These values were identified from publicly-available studies and unpublished studies submitted to EPA's Office of Prevention, Pesticides, and Toxic Substances. Although dose spacing among these intermediate-duration oral studies is variable, and in some studies may be in excess of 100-fold for levels at or below identified LOAELs for AChE inhibition, these studies collectively indicate that the threshold for less serious AChE inhibition occurs in rats and dogs at repeated oral dose levels between 0.2 and 2 mg/kg/day.

In selecting the principal study for deriving an intermediate-duration oral MRL for diazinon, one 6-week oral rat study (Trutter 1991) employed relatively narrow dose spacing in the region of 0.2–2 mg/kg/day

Table 2-3. NOAELs and LOAELs for RBC and Brain AChE Inhibition Following Intermediate-duration Dietary Exposure to Diazinon

Study type estimated doses (mg/kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day) AChE inhibition	Reference
28-Day rat study	0.02 (M, F)	2.4; M, F: 38–59% RBC	EPA 1996
M, F: 0, 0.02, 2.4, 23, 213			
30-Day rat study	ND	2.86; 58% RBC	Davies and Holub 1980b
F: 0, 2.86			
35-Day rat study	0.2	ND	Davies and Holub 1980a
F: 0, 0.009, 0.05, 0.09, 0.2			
42-Day rat study	0.18	0.27; 20% RBC	Davies and Holub 1980a
F: 0, 0.09, 0.18, 0.27, 0.36			
6-Week rat study			Trutter 1991
M: 0, 0.018, 0.045, 0.19, 1.81, 9.08, 26.67	0.19 (M)	1.81; M: 46–55% RBC	
F: 0, 0.02, 0.038, 0.20, 1.97, 9.78, 30.20	0.20 (F)	1.97; F: 50–61% RBC	
6-Week rat study			Makhteshim-Agan 1989
M: 0, 0.02, 0.04, 0.17, 1.68, 8.60, 25.76	0.17 (M)	1.68; M: 29–35% RBC	
F: 0, 0.02, 0.05, 0.19, 1.82, 9.27, 28.95	0.19 (F)	1.82; F: 16–35% RBC	
6-Week rat study	0.2 (M, F)	8.4; M: 21% RBC	Singh 1988
M: 0, 0.04, 0.2, 8.4, 150.8			
F: 0, 0.05, 0.2, 9.4, 198		9.4; F: 21% RBC and 24% brain	
90-Day rat study			Singh 1988
M: 0, 0.03, 0.3, 15, 168	0.3 (M)	15; M: 27% RBC	
F: 0, 0.04, 0.4, 19, 212	0.4 (F)	19; F: 41% RBC	
90-Day rat study	0.018 (M, F)	1.8; M, F: 37–75% RBC	EPA 1996
0, 0.018, 1.8, 18, 180			
92-Day rat study	0.4	0.8; 40% RBC	Davies and Holub 1980a
F: 0, 0.4, 0.8, 1.2			
4-Week dog study			Barnes 1988
M: 0, 0.02, 0.073, 0.8, 14.68	0.8 (M)	14.68; M: 25% RBC; 31% brain	
F: 0, 0.023, 0.082, 0.75, 15.99	0.75 (F)	5.6; F: 31% RBC; 30% brain	
13-Week dog study	0.02 (M, F)		Barnes 1988
M: 0, 0.0034, 0.02, 5.9, 10.9		5.9; M: 26% RBC; 31% brain	
F: 0, 0.0037, 0.02, 5.6, 11.6		5.6; F: 31% RBC ; 30% brain	

AChE = acetylcholinesterase; F = female; LOAEL = lowest-observed-adverse-effect level; M = male; ND = not determined; NOAEL = no-observed-adverse-effect level; RBC = red blood cell

and was initially considered as a candidate for deriving an intermediate-duration oral MRL for diazinon. However, the three lowest dose groups inadvertently received essentially no diazinon in the diet during treatment week 5, thus precluding the usefulness of the study results for purposes of quantitative risk assessment. The 90-day oral rat study of Singh (1988) was considered as a candidate for the principal study because (1) it identified the highest NOAEL (0.3 mg/kg/day for males and 0.4 mg/kg/day for females) below the lowest LOAELs identified in other repeated-dose oral studies, and (2) quantitative dose-response data for the critical effect (RBC AChE inhibition) were available for BMD analysis. The 42-day oral rat study of Davies and Holub (1980a) was considered because the effects of diazinon on RBC AChE inhibition were assessed at several doses within the low-dose range (0.1–0.4 mg/kg/day). This study identified a NOAEL of 0.18 mg/kg/day and a LOAEL of 0.27 mg/kg/day for 20% RBC AChE inhibition.

In the study of Singh (1988), groups of male and female Sprague-Dawley rats (15/sex) were administered diazinon MG-8 (purity 87.7%) in the diet at concentrations of 0, 0.5, 5, 250, or 2,500 ppm (after adjusting for purity) for 90 days. The corresponding doses were calculated by the study authors to be 0.03, 0.3, 15, and 168 mg/kg in males and 0.04, 0.4, 19, and 212 mg/kg in females. Clinical observations were made daily and body weight and food consumption were recorded weekly. Clinical laboratory measurements and physical, auditory, and ophthalmoscopic exams were performed prior to termination. Prior to necropsy, blood and urine samples were collected for hematology, clinical chemistry, and urinalysis. At necropsy, organ weights were recorded and comprehensive gross and microscopic examinations were performed on all rats. A portion of each brain was processed for assessment of AChE activity. All animals survived the 90-day dosing period. Treatment-related clinical symptoms were observed at the highest dose level and included hyperactivity and hypersensitivity to touch and sound in males and females and aggressive behavior in males. No treatment-related gross or microscopic abnormalities were seen in any of the treatment groups. Hematology and urinalysis were unremarkable, with the exception of decreased mean hemoglobin and hematocrit accompanied by an increase in reticulocytes in high-dose females. Statistically-significant ($p<0.01$) effects on ChE and AChE included decreased plasma ChE activity in males and females at doses ≥0.3 mg/kg/day, decreased RBC AChE activity at doses ≥15 mg/kg/day in males and ≥0.4 mg/kg/day in females, and decreased brain AChE activity at the highest dose in males and doses ≥19 mg/kg/day in females. As discussed earlier, a 20–59% inhibition (reduction in measured activity) of neural or RBC AChE may be considered a less serious effect in the absence of more serious indicators of neurotoxicity (Chou and Williams-Johnson 1998). Treatment-related decreased RBC activity was noted at doses lower than those resulting in decreased brain AChE activity

and was therefore selected as the critical effect for BMD analysis. Table 2-4 contains the data that were modeled.

The linear model in the EPA Benchmark Dose Software (Version 1.3.2) was initially fit to the male rat data for RBC AChE activity shown in Table 2-4. A benchmark response (BMR) of 20% below the control mean RBC AChE activity was selected because 20–59% RBC or brain AChE inhibition is considered to represent a less serious effect in the absence of more serious indicators of neurotoxicity (Chou and Williams-Johnson 1998).

Inadequate fit was provided by the linear model, as indicated by a p value <0.0001 for the test of mean fit (according to BMD technical guidance, a p value ≥0.1 indicates an adequate goodness-of-fit). The same result was obtained using the BMD software for the polynomial and power models. The BMD software for the Hill model calculated a BMD_{20} of 0.38 mg/kg/day for the male rat data, but failed to identify the lower 95% confidence limit ($BMDL_{20}$) value (presumably due to a bad completion code in an optimization routine). Under the presumption that the highest dose may have been a major influence in the model output, the data from the highest dose were eliminated and the linear model was fit to the remaining data. In this case, a near-adequate fit was obtained, as indicated by a p value of 0.09294 for the test of mean fit. The polynomial and power model outputs from the male rat data set (minus the highest dose) were found to be clearly inadequate, based on p values of 0.02919 and 0.02928 for the test of mean fit. Without the high-dose data, the data set for RBC AChE activity in the male rats of the Singh (1988) study contained insufficient dose groups to accommodate the requirements for the Hill model. In summary, the results of BMD analysis of RBC AChE activity in the male rats of the Singh (1988) study were rejected due to inadequate fit from all available continuous data models in the EPA Benchmark Dose Software (Version 1.3.2).

For the female rat data (see Table 2-4), inadequate fit was provided by the linear, polynomial, and power models, as indicated by p values <0.0001 for the test of mean fit. The Hill model provided the only adequate fit of the female data and resulted in a BMD_{20} of 0.56 mg/kg/day and a $BMDL_{20}$ of 0.38 mg/kg/day. Elimination of the RBC AChE activity data for the highest-dose female rats did not result in adequate fit for the linear, polynomial, or power models. Furthermore, this elimination resulted in insufficient dose groups to accommodate the requirements of the Hill model. In summary, BMD analysis of RBC AChE activity in the female rats of the Singh (1988) study resulted in a single adequate fit (Hill model output using all dose groups) and resulting BMD_{20} of 0.56 mg/kg/day and a $BMDL_{20}$ of 0.38 mg/kg/day.

Table 2-4. RBC AChE Data From Male and Female Rats Exposed to Diazinon in the Diet for 90 Days

Dose group (mg/kg/day)	Number of rats	RBC AChE activity (mU/mL)[a]	Percent RBC AChE inhibition
Males			
0	15	2093.333±44.150	
0.03	15	2186.667±68.220	–
0.3	15	2000.000±59.362	4
15	15	1526.667±58.119	27
168	15	1540.000±60.788	26
Females			
0	14	2300.000±58.366	
0.04	15	2213.333±46.667	4
0.4	15	1913.333±45.635	17
19	15	1353.333±40.079	41
212	15	1346.667±33.618	41

[a]Mean±standard error

Source: Singh 1988

In the study of Davies and Holub (1980a), groups of female Wistar rats (16/group) were exposed to diazinon (99.2% purity) in the diet at concentrations of 0, 1, 2, 3, or 4 ppm for 42 days. Blood samples were collected periodically from 10 rats/group for assessment of plasma ChE and RBC AChE activity. Six rats per group were sacrificed on day 35 for assessment of brain AChE activity. All rats were assessed daily for clinical signs of neurotoxicity and body weights and food intake were monitored throughout the treatment period. Based on reported food consumption and body weight data, the doses to the 1-, 2-, 3-, and 4-ppm exposure groups were calculated to be 0.09, 0.18, 0.27, and 0.36 mg/kg/day. No clinical signs of toxicity were observed in any of the treated groups. Significant plasma ChE inhibition was observed at most timepoints in all diazinon-treated groups, relative to controls. The magnitude of inhibition in all treatment groups increased with time and appeared to peak around day 35, remaining near the peak level for the remaining 7 treatment days. Maximum plasma ChE inhibition in the 0.09, 0.18, 0.27, and 0.36 mg/kg/day treatment groups was approximately 35, 50, 55, and >60%, respectively. Plasma ChE inhibition is used as an indicator of exposure, but does not serve as a reliable indicator of a neurotoxic effect. Therefore, plasma ChE inhibition was not considered relevant to the selection of the critical effect for diazinon. Through treatment day 35, there was no significant treatment-related effect on RBC AChE activity in any of the treatment groups. However, on treatment day 42, significant RBC AChE inhibition was observed at treatment levels of 0.18, 0.27, and 0.36 mg/kg/day (magnitude 9, 20, and 22%, respectively). There were no indications of treatment-related significant brain AChE inhibition at any timepoint during the 42 days of treatment. The results of RBC AChE activity in the female rats of the principal study (Davies and Holub 1980a) are presented in Table 2-5. Inhibition of RBC AChE and brain AChE represents a relevant neurological effect. Treatment-related 20–59% RBC or brain AChE inhibition is considered to represent a less serious adverse effect in the absence of more clear indicators of neurotoxicity (Chou and Williams-Johnson 1998). The principal study (Davies and Holub 1980a) identified a NOAEL of 0.18 mg/kg/day and a LOAEL of 0.27 mg/kg/day for 20% RBC AChE inhibition in female rats administered diazinon in the diet for 42 days.

The linear model in the EPA Benchmark Dose Software (Version 1.3.2) was fit to the female rat data. As discussed previously, a BMR of 20% below the control mean RBC AChE activity was selected because 20–59% RBC or brain AChE inhibition is considered to represent a less serious effect in the absence of more serious indicators of neurotoxicity (Chou and Williams-Johnson 1998). Initial BMD analysis using the linear model was performed using constant variance as one of the selected parameters. The model output indicated that a nonhomogeneous variance was more appropriate for the data set. Using a nonhomogeneous variance, the linear model provided adequate fit to the data from Table 2-5, as indicated by acceptable p values for tests for (1) differences in response and/or variances among dose levels,

Table 2-5. RBC AChE Data From Female Rats Exposed to Diazinon in the Diet for 42 Days

Dose group (mg/kg/day)	Number of rats	RBC AChE activity (µmole/mL packed cells/minute)[a]	Percent RBC AChE inhibition
0	10	0.74±0.05	
0.09	10	0.68±0.07	8
0.18	10	0.67±0.06	9
0.27	10	0.59±0.04	20
0.36	10	0.58±0.02	22

[a]Mean±standard error

AChE = acetylcholinesterase; RBC = red blood cell

Source: Davies and Holub 1980a

(2) homogeneous or nonhomogeneous variance, and (3) model mean fit. The resulting BMD_{20} was 0.36 mg/kg/day and the $BMDL_{20}$ was 0.25 mg/kg/day. Because the simplest model, the linear model, provided adequate fit to the RBC AChE data from the 42-day rat study of Davies and Holub (1980a), the application of more complex continuous variable models was not considered necessary.

BMD analysis identified two potential points of departure for deriving an intermediate-duration oral MRL for diazinon, the $BMDL_{20}$ of 0.3267 mg/kg/day for RBC AChE activity in the female rats from the 90-day oral rat study of Singh (1988) and the $BMDL_{20}$ of 0.2238 mg/kg/day for RBC AChE activity in the female rats from the 42-day oral study of Davies and Holub (1980a). The 42-day oral rat study of Davies and Holub (1980a) was selected as the principal study based on the fact that this study employed several dose groups in the low-dose region of threshold effect. Therefore, the $BMDL_{20}$ of 0.2238 mg/kg/day from the RBC AChE data of Davies and Holub (1980a) was selected as the point of departure for deriving an intermediate-duration oral MRL for diazinon. The $BMDL_{20}$ of 0.2238 mg/kg/day was divided by an uncertainty factor (UF) of 100 (10 for extrapolation from animals to humans and 10 for human variability) resulting in an intermediate-duration oral MRL of 0.002 mg/kg/day.

- An MRL of 0.0007 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to diazinon.

The chronic-duration oral MRL is based on a NOAEL of 0.065 mg/kg/day and a LOAEL of 5.5 mg/kg/day for >20% RBC AChE inhibition in female rats administered diazinon in the diet for 98 weeks (Kirchner et al. 1991).

No human data are available from which to evaluate the health effects associated with chronic-duration oral exposure to diazinon. The available chronic-duration oral database in animals consists of two unpublished studies, a 98-week feeding study in rats and a 52-week feeding study in dogs. These studies identified RBC AChE inhibition as the most sensitive effect of diazinon toxicity.

The 52-week dog study (Rudzki et al. 1991) identified a NOAEL of 0.5 ppm (0.017 mg/kg/day) and a LOAEL of 150 ppm (4.6 mg/kg/day) for RBC AChE inhibition of 20% or more in both males and females at treatment day 359. The 98-week rat study (Kirchner et al. 1991) identified a NOAEL of 0.065 mg/kg/day and a LOAEL of 5.5 mg/kg/day for RBC AChE inhibition of 20% or more in both males and females. The 98-week rat study (Kirchner et al. 1991) was selected as the principal study for deriving a chronic-duration oral MRL for diazinon because: (1) clinical chemistry results, including assessments of AChE inhibition, were available for a treatment period in excess of 364 days and (2) the

study identified a slightly higher NOAEL (0.065 mg/kg/day) than the NOAEL (0.017 mg/kg/day) identified in the 52-week dog study (Rudzki et al. 1991).

In the 98-week rat study (Kirchner et al. 1991), diazinon MG-8 (purity 87.7%) was dissolved in acetone vehicle and added to the diet of male and female Sprague-Dawley rats at concentrations of 0, 0.1, 1.5, 125, or 250 ppm for up to 98 weeks. The study included both untreated and vehicle control groups. According to the study authors, the corresponding diazinon doses (adjusted for purity) were 0, 0.004, 0.06, 5, and 10 mg/kg/day for males and 0, 0.005, 0.07, 6, and 12 mg/kg/day for females), which result in averaged doses of 0, 0.0045, 0.065, 5.5, and 11 mg/kg/day for both males and females. Twenty rats/sex/group were treated for the full 98 weeks. Ten rats/sex/group were treated for 52 weeks and sacrificed for interim assessment. Additional groups of 10 rats/sex were assigned to the untreated control, vehicle control, and 250 ppm groups and assessed for recovery 45 days following 52 weeks of treatment. Animals were observed daily for clinical signs of toxicity. Food consumption, water intake, and body weights were monitored. Ophthalmoscopic examinations were performed during weeks 2, 51, and 97 or 98. Blood was collected on at several timepoints between days 88 and 684. Ten animals/sex/group from the 98-week treatment groups received clinical chemistry evaluation at treatment days 88, 181, 356, 390, 552, and 684. Urinalysis was performed on all surviving rats of the 98-week treatment groups at treatment days 81, 189, 350, 545, and 679. All rats were subjected to comprehensive gross and microscopic pathologic examination at death or sacrifice. There were no apparent treatment-related effects on survival, food or water consumption, body weights, or hematological or urinalysis parameters examined. Due to mortality in all groups, including controls, the study was terminated at 97 weeks. Ophthalmoscopic and gross and microscopic examinations did not reveal evidence of dose-related effects. The major findings of this study were those of dose related decreased plasma ChE and RBC and brain AChE activity in both male and female rats. Significantly decreased plasma ChE activity (28–51% lower than controls) was noted in 0.065 mg/kg/day male rats at treatment days 88 and 684, but not at treatment days 181, 356, or 552 and in 0.065 mg/kg/day female rats (approximately 50% lower than controls) at most timepoints. High-dose male and female rats consistently exhibited significantly decreased plasma ChE activity, ranging from 80 to 97% lower than controls. In 0.065 mg/kg/day groups, RBC and brain AChE activity was not significantly decreased at any timepoint. The 5.5 mg/kg/day groups exhibited significantly decreased RBC AChE activity at all timepoints, ranging in magnitude from 15 to 28% and from 22 to 25% in males and females, respectively. At the 5.5 and 11 mg/kg/day levels, the magnitude of the effect did not appear to increase with either duration of treatment or increased dose. Following 52 weeks of treatment and 45 days of recovery, RBC AChE activity had returned to control levels in high-dose male rats and to within 7% of control levels in high-dose female rats. Brain AChE activity was

significantly decreased in 5.5 and 11 mg/kg/day male and female rats. In 5.5 and 11 mg/kg/day males, the magnitude of the effect was effect was 24 and 42%, respectively, after 684 days of treatment, but not significantly different from controls at 370 days. In 5.5 and 11mg/kg/day female rats, the effect was noted at both 370 and 684 day timepoints; the magnitude of the effect was >24% at 5.5 mg/kg/day and >40% at 11 mg/kg/day.

All available continuous variable models in the EPA Benchmark Dose Software (Version 1.3.2) were fit to the male and female rat data for RBC AChE activity reported in the principal study (Kirchner et al. 1991). A benchmark response (BMR) of 20% below the control mean RBC AChE activity was selected because 20–59% RBC or brain AChE inhibition is considered to represent a less serious effect in the absence of more serious indicators of neurotoxicity (Chou and Williams-Johnson 1998). Inadequate mean fit was provided by all models, as indicated by p values <0.05 for tests of mean fit (according to BMD technical guidance, a p value ≥0.1 indicates an adequate goodness-of-fit). Because BMD analysis provided inadequate mean fit to the RBC AChE data sets, a NOAEL/LOAEL approach was taken to derive a chronic-duration oral MRL for diazinon. The principal study (Kirchner et al. 1991) identified a NOAEL of 0.065 mg/kg/day (1.5 ppm of diazinon in the diet) and a LOAEL of 5.5 mg/kg/day (125 ppm of diazinon in the diet) for 22–28% decreased RBC AChE activity in male and female rats, which is considered the critical effect. The effect was observed as early as day 88 of treatment and did not appear to increase in magnitude with duration of treatment. The NOAEL of 0.065 mg/kg/day was divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) resulting in a chronic-duration oral MRL of 0.0007 mg/kg/day.

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 diazinon. 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.

Systemic effects common to humans and laboratory animals exposed to diazinon by all natural exposure routes (inhalation, oral, dermal) are primarily attributable to the inhibition of acetylcholinesterase (AChE) by diazoxon, the active metabolite of diazinon. Inhibition of AChE at nerve terminals in central and peripheral nervous tissues triggers cholinergic signs and symptoms that are particularly apparent in respiratory, cardiovascular, and gastrointestinal systems. Although listed under specific systemic effects sections, many of the systemic effects listed are likely the direct result of AChE inhibition. Some cases of human exposure to diazinon may include mixed (inhalation, oral, and/or dermal) exposure routes; in such cases, a cumulative dose of diazinon would be expected to be the result of absorption by all relevant exposure routes.

The Toxicological Profile for Diazinon deals with diazinon-induced health effects in humans and animals. Most controlled animal studies were performed using technical-grade diazinon (purity ranging from 87 to essentially 100%). Other ingredients in technical-grade diazinon were not typically specified. Some animal studies employed particular diazinon pesticide formulations such as 60EC (a 60% emulsifiable concentration of diazinon) or 25WP (a 25% wettable powder). Summaries of animal data in the Toxicological Profile for Diazinon focus on health effects in animals exposed to technical-grade diazinon. MRLs were derived from results of studies that employed technical-grade diazinon. Available controlled human studies were performed using technical-grade diazinon of high purity. However, most of the available human data derive from case reports of intentional or accidental exposure to various diazinon formulations. Exposure of pesticide applicators often included exposure to other pesticides as well. Thus, some signs and symptoms resulting from a particular exposure scenario may be at least partly attributable to compounds other than diazinon. Furthermore, the extent and rate of absorption of diazinon may vary greatly depending on the source of diazinon exposure (i.e., technical grade or particular formulation of an end-use product).

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.

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.

The principal toxic effect of diazinon in humans and laboratory animals is inhibition of acetylcholinesterase (AChE), which results in the accumulation of acetylcholine at acetylcholine receptors leading to cholinergic responses in the peripheral (muscarinic and nicotinic) and central nervous system and neuromuscular junctions. In this Toxicological Profile for Diazinon, AChE inhibition of magnitude 20–59% is considered a less serious adverse effect in the absence of more serious signs of neurotoxicity. AChE inhibition ≥60% is considered a more serious effect independent of the presence or absence of other neurotoxicity indicators.

3.2.1 Inhalation Exposure

Diazinon has a low volatility; thus, inhalation exposure is likely to be to diazinon aerosols rather than vapor. In one of the studies described below, animals were exposed to diazinon in inhalation chambers (Holbert 1989). It is possible that some of the exposure under these conditions was by the dermal route and/or the oral route (grooming).

3.2.1.1 Death

There are no reports of deaths in humans or animals exposed by inhalation to diazinon alone. One case report described the death and autopsy results of a 51-year-old man who had been exposed to an insecticide mixture that contained diazinon and malathion, another anticholinesterase insecticide that is more acutely potent than diazinon (Wecker et al. 1985). The death was attributed to irreversible cardiac arrest, despite atropine therapy. Autopsy revealed mild pathologic changes in intercostal muscle tissue, including muscle fibers with subsarcolemmal grouped granular basophilic inclusions and scattered areas of necrosis. The victim's neuromuscular AChE activity was one-half that of muscle from unexposed persons.

No deaths were reported in Sprague-Dawley rats (5/sex) exposed to 2,330 mg/m^3 diazinon for 4 hours in inhalation chambers and observed for a further 14 days (Holbert 1989), or in hybrid rats (10/sex/group) exposed to air concentrations of 0.05, 0.46, 1.57, or 11.6 mg/m^3 diazinon (nose-only) for 6 hours/day, 5 days/week for 3 weeks (Hartman 1990).

3.2.1.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, dermal, ocular, or body weight effects in humans after inhalation exposure to diazinon. A single study described mild degenerative changes in the muscles in a human acute-duration exposure to a mixture of diazinon and malathion (Wecker et al. 1985). No studies were located regarding gastrointestinal, musculoskeletal, or dermal effects in animals after inhalation exposure to diazinon. The systemic effects observed in humans and animals after inhalation exposure to diazinon are discussed below. The highest NOAEL and all LOAEL values from each reliable study for systemic end points in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Nasal discharge was observed in Sprague-Dawley rats exposed to 2,330 mg/m^3 diazinon for 4 hours in an inhalation chamber (Holbert 1989). A statistically significant increase in lung-to-body weight ratio was observed in hybrid female rats exposed to 0.46 and 1.57 mg/m^3 diazinon (nose-only) for 6 hours/day, 5 days/week for 3 weeks (Hartman 1990). This effect was not seen in male rats or in female rats exposed at 11.6 mg/m^3, so its toxicological significance is unclear. No gross or histological evidence of treatment-related damage to nasal tissues or the lungs was observed at the termination of this study.

Cardiovascular Effects. No gross or histological evidence of treatment-related damage to the heart was observed in hybrid rats (10/sex) exposed to 11.6 mg/m^3 diazinon (nose-only) 6 hours/day, 5 days/week for 3 weeks (Hartman 1990).

Hematological Effects. No statistically significant effects on hematological parameters (erythrocyte count, hemoglobin, packed red cell volume) were seen in hybrid rats (10/sex/group) exposed to up to 11.6 mg/m^3 diazinon (nose-only) for 6 hours/day, 5 days/week for 3 weeks (Hartman 1990).

Musculoskeletal Effects. Mild pathologic changes in the intercostal muscle tissue, including muscle fibers with subsarcolemmal grouped granular basophilic inclusions and scattered areas of necrosis were reported in the autopsy of a 51-year-old man who died from high acute-duration exposure, via inhalation, to a commercial insecticide spray containing diazinon and malathion. Neuromuscular AChE activity was one-half that of muscle from unexposed persons (Wecker et al. 1985).

Table 3-1 Levels of Significant Exposure to Diazinon - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Systemic								
1	Rat (Sprague-Dawley)	4 hr	Resp		2330 M (nasal discharge; 3/5)		Holbert 1989	
			Renal		2330 F (polyuria; 3/5)			
			Bd Wt	2330				
Neurological								
2	Rat (Sprague-Dawley)	4 hr			2330 (decreased activity, 2/5; salivation, 2/5)		Holbert 1989	
INTERMEDIATE EXPOSURE								
Systemic								
3	Rat (Hybrid)	3 wk 5 d/wk 6 hr/d	Resp	11.6			Hartman 1990	
			Cardio	11.6				
			Hemato	11.6				
			Hepatic	11.6				
			Renal	11.6				
			Endocr	11.6				
			Ocular	11.6				
			Bd Wt	11.6				
Immuno/ Lymphoret								
4	Rat (Hybrid)	3 wk 5 d/wk 6 hr/d		11.6			Hartman 1990	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
Neurological								
5	Rat (Hybrid)			1.57[b]	11.6 (36-39% RBC AChE inhibition)		Hartman 1990	

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

b Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.01 mg/m3 for diazinon. The concentration (1.57 mg/m3) was adjusted for intermittent exposure and converted to a human equivalent concentration as described in detail in Appendix A. The resulting duration-adjusted human equivalent concentration was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability).

AChE = acetylcholinesterase; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; RBC = red blood cell; Resp = respiratory; wk = week(s)

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

Acute (≤14 days)

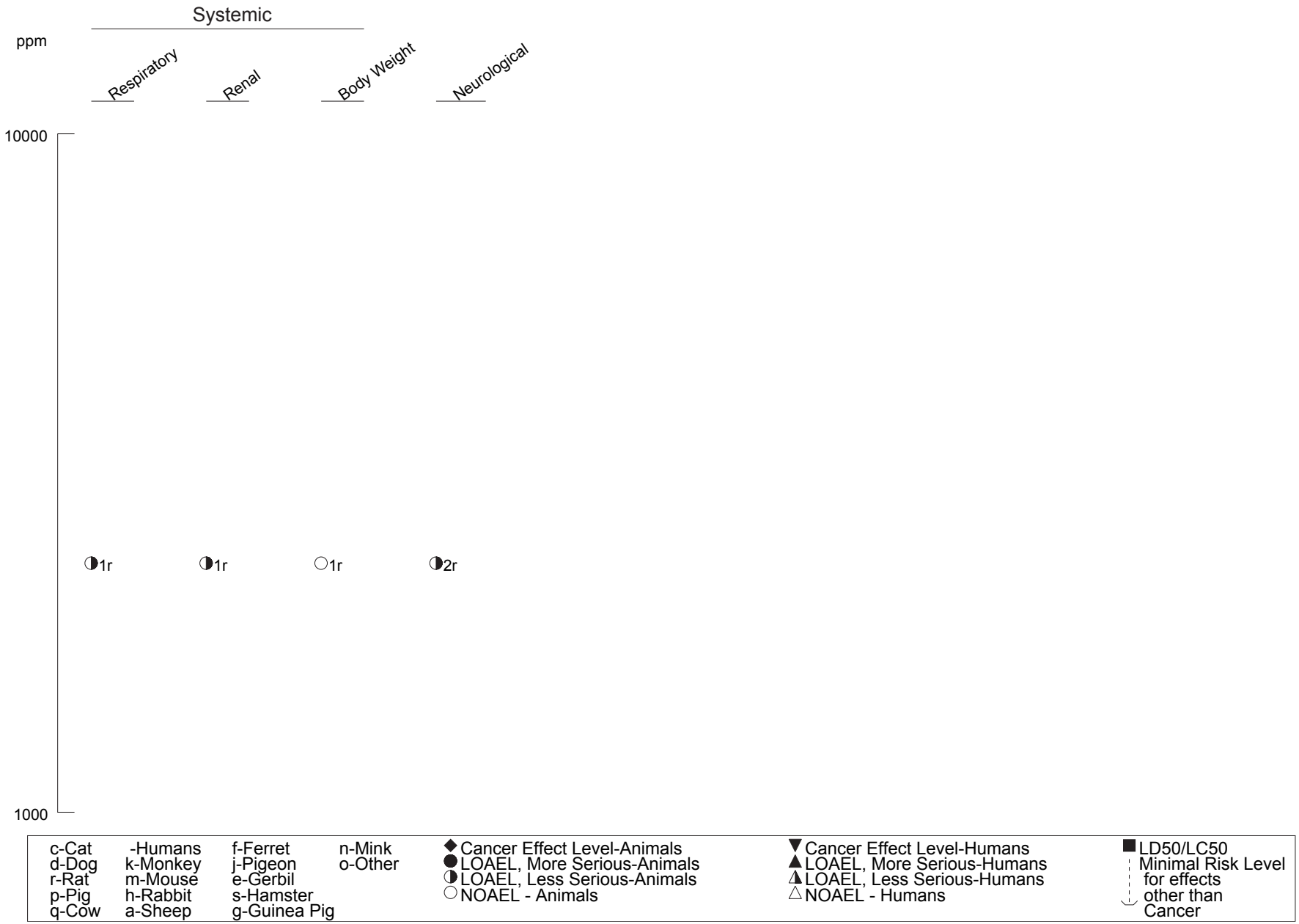
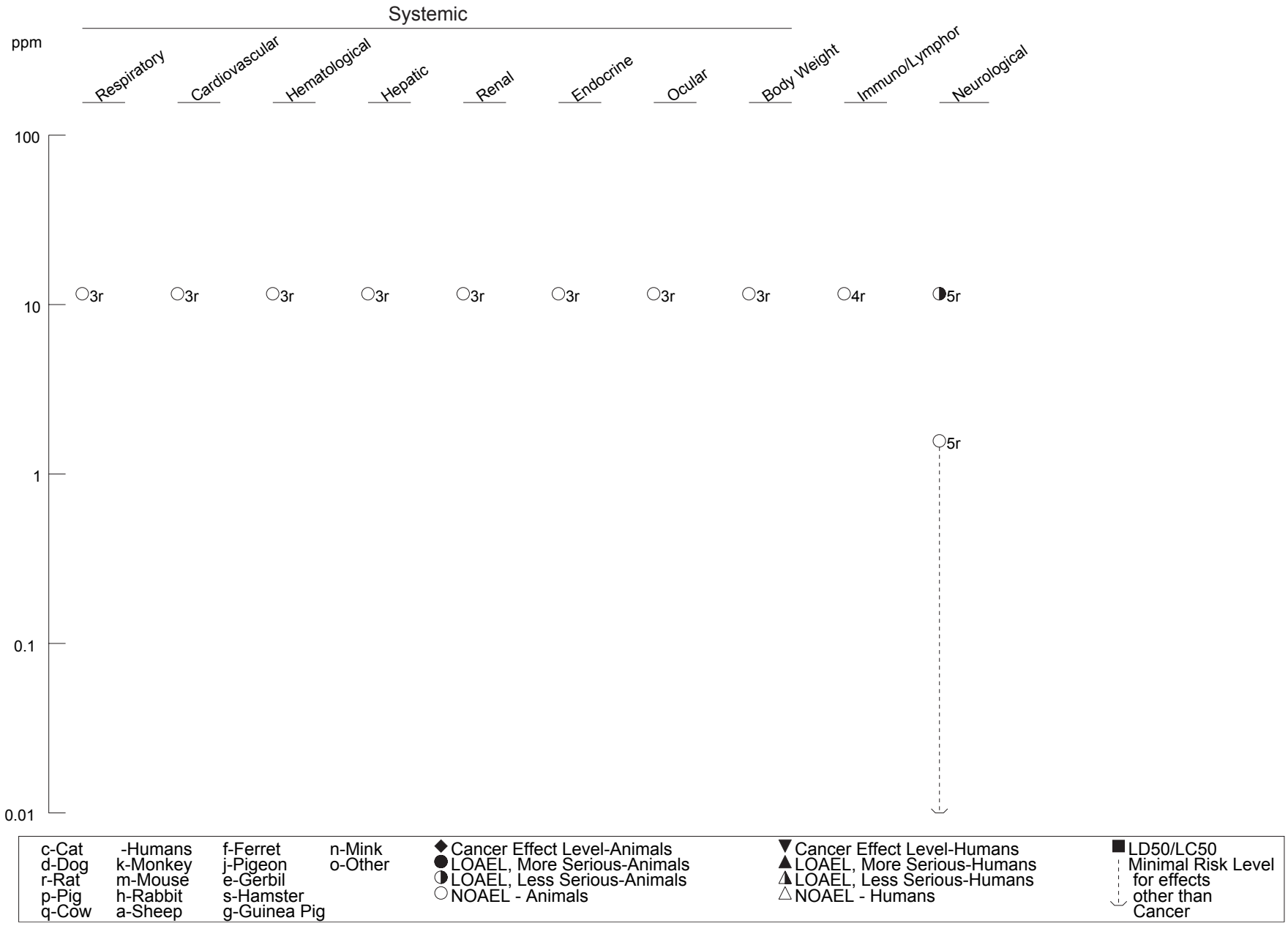


Figure 3-1 Levels of Significant Exposure to Diazinon - Inhalation *(Continued)*

Intermediate (15-364 days)



Hepatic Effects. No gross or histological evidence of treatment-related damage to the liver was observed in hybrid rats (10/sex) exposed to 11.6 mg/m^3 diazinon (nose-only) for 6 hours/day, 5 days/week for 3 weeks (Hartman 1990).

Renal Effects. Polyuria was observed in Sprague-Dawley rats exposed to 2,330 mg/m^3 diazinon for 4 hours (Holbert 1989). No gross or histological evidence of treatment-related damage to the kidney was observed in hybrid rats (10/sex) exposed to 11.6 mg/m^3 diazinon (nose-only) for 6 hours/day, 5 days/week for 3 weeks (Hartman 1990).

Endocrine Effects. No gross or histological evidence of treatment-related damage to the adrenal gland was observed in hybrid rats (10/sex) exposed to 11.6 mg/m^3 diazinon (nose-only) for 6 hours/day, 5 days/week for 3 weeks (Hartman 1990).

Ocular Effects. Ptosis was observed in Sprague-Dawley rats exposed to 2,330 mg/m^3 diazinon for 4 hours in an inhalation chamber (Holbert 1989). No evidence of treatment-related ophthalmoscopic lesions was observed in hybrid rats (10/sex/group) exposed to up to 11.6 mg/m^3 diazinon (nose-only) for 6 hours/day, 5 days/week for 3 weeks (Hartman 1990).

Body Weight Effects. No effect on body weight was observed in Sprague-Dawley rats (5/sex) exposed to 2,330 mg/m^3 diazinon for 4 hours and observed for 14 days (Holbert 1989) or in hybrid rats (10/sex/group) exposed to up to 11.6 mg/m^3 diazinon (nose-only) for 6 hours/day, 5 days/week for 3 weeks (Hartman 1990).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans after inhalation exposure to diazinon.

No gross or histological evidence of treatment-related damage to the spleen was observed in hybrid rats (10/sex) exposed to 11.6 mg/m^3 diazinon (nose-only) for 6 hours/day, 5 days/week for 3 weeks (Hartman 1990).

The NOAEL for immunological and/or lymphoreticular end points in hybrid rats for intermediate-duration exposure is recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.4 Neurological Effects

Diazinon, an anticholinesterase organophosphate, inhibits AChE in the central and peripheral nervous system. Inhibition of AChE results in accumulation of acetylcholine at muscarinic and nicotinic receptors leading to peripheral and central nervous system effects. These effects usually appear within a few minutes to 24 hours after exposure, depending on the extent of exposure. Most of the located reports of incidents of human exposure to diazinon involved occupational exposure via the inhalation route, although it is possible that significant exposure also took place via the dermal route.

Cholinergic symptoms began within 15 minutes in 17 of 18 mushroom workers exposed to diazinon sprayed around the only entrance to a room in which they were working. The workers exhibited reduced plasma cholinesterase (ChE) and erythrocyte acetylcholinesterase (RBC AChE) levels (markers for diazinon exposure) within 48 hours; plasma ChE levels were inhibited 27–29% by diazinon exposure during 15 days postexposure (Coye et al. 1987). In another report, members of a family complained of signs and symptoms of insecticide poisoning (headache, vomiting, fatigue, chest heaviness) after moving into a house that had been treated with diazinon. Five months after the diazinon treatment, analysis of the family members' urine samples showed "very high urinary levels" (0.5–1.5 mg/L) of a diazinon metabolite, diethylphosphate (DEP), while plasma ChE levels were slightly depressed (79–94% of normal levels). Surface concentrations of diazinon in the home ranged from 126 to 1,051 $\mu g/m^2$, air concentrations were between 5 and 27 $\mu g/m^3$, and some clothing showed contamination (0.5–0.7 μg/g). After cleanup of the house, the signs and symptoms reported by family members promptly ceased, and the urinary excretion of DEP dropped to background levels (Richter et al. 1992). Another case study of 99 individuals who were occupationally exposed to diazinon granules 8 hours/day for 39 days during an insecticide application program reported only slight neurological functional deficits (postshift symbol-digit speed and pattern memory accuracy) as a result of the exposure. A dose of 0.02 mg/kg/day, considered a NOAEL, was estimated for the workers on the basis of measured diazinon concentration in passive dermal badges, hand rinses, and full-shift breathing-zone air samples. Thus, multiple exposure routes were implied, making it difficult to verify the dose calculated by the authors of the study. Adequate information regarding exposure time to onset and recovery (if any) from the slight neurological functional deficits described was not provided in the report (Maizlish et al. 1987). Other persons occupationally exposed to organophosphorus insecticides, including diazinon, showed no significant change in neurological function, although there was a reduction in plasma ChE levels indicating exposure (Stalberg et al. 1978). In contrast, organophosphate-induced increases in hyperreflexia were reported in

workers occupationally exposed to many insecticides, including diazinon. These workers, however, showed no overt signs of poisoning or of cholinergic signs and symptoms after spraying diazinon (Rayner et al. 1972). Two other insecticide sprayers developed cholinergic symptoms after spraying diazinon. Symptoms included nausea, vomiting, muscle twitching, difficulty breathing, and blurred vision. Plasma ChE and RBC AChE activities remained depressed for at least 18 days after exposure (Soliman et al. 1982). In all of these cases of occupational exposure (Rayner et al. 1972; Soliman et al. 1982; Stalberg et al. 1978), no estimate of the exposure level to diazinon was made.

A 42-year-old woman (26 weeks pregnant) in the country of Qatar was exposed when she used undiluted diazinon liquid insecticide (60EC) to clean a nonventilated bathroom (Kamha et al. 2005). Her symptoms included dizziness, vomiting, blurred vision, and increased salivation. Laboratory tests revealed plasma ChE activity of 161 U/L (normal range 5,400–13,200 U/L), which confirmed a clinical diagnosis of organophosphate poisoning. The patient was treated with the cholineaterase reactivators atropine and 2-PAM (pralidoxime) and the symptoms of diazinon poisoning subsided.

Decreased activity and salivation were noted in Sprague-Dawley rats exposed to 2,330 mg/m^3 diazinon for 4 hours in an inhalation chamber (Holbert 1989). No clinical signs of neurological effects except piloerection were observed in hybrid rats exposed to 0.05, 0.46, 1.57, or 11.6 mg/m^3 diazinon for 6 hours/day, 5 days/week for 3 weeks (Hartman 1990). At study termination, plasma ChE activity (a marker for diazinon exposure) was significantly decreased in a dose-related manner in females. Decreases of 20, 27, and 43% were seen at airborne diazinon levels of 0.46, 1.57, and 11.6 mg/m^3, respectively. No change was seen at 0.05 mg/m^3. In males, no change was seen at 0.05 or 0.46 mg/m^3, but decreases of 14 and 19% were seen at 1.57 and 11.6 mg/m^3, respectively. RBC AChE activity (a surrogate marker for neural AChE) was unaffected in females at 0.05 and 0.46 mg/m^3, but was decreased by 10 and 39% at 1.57 and 11.6 mg/m^3, respectively. In males, no change was seen at 0.05, 0.46, or 1.57 mg/m^3, while a decrease of 36% was observed at 11.6 mg/m^3. Brain AChE activity was unchanged in males at all exposure levels, but was decreased in females at 0.05 mg/m^3 (24%), 0.46 mg/m^3 (17%), 1.57 mg/m^3 (20%), and 11.6 mg/m^3 (37%). The decreases in the females at the two lowest exposures are unusual in that no accompanying decrease in RBC AChE activity was observed. Diazinon exposure had a consistently greater effect on cholinesterase activities in females than in males in this study, although clinical signs of neurological effects (other than piloerection) were not observed in either sex.

No studies were located regarding organophosphate-induced delayed neurotoxicity (OPIDN) in humans or in animals after inhalation exposure to diazinon.

The highest NOAEL and all LOAEL values from each reliable study for neurological end points in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after inhalation exposure to diazinon.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to diazinon.

3.2.1.7 Cancer

Several epidemiological studies have reported increased incidence of cancers in humans who were concurrently or sequentially exposed to a number of insecticides, including diazinon. Some of the exposure is presumed to have occurred by the inhalation route. Because epidemiological studies typically involve exposure to multiple pesticides, the carcinogenicity of diazinon itself has not been determined.

A case-control study suggested a possible link between family gardening use of diazinon (and other insecticides) and increased incidence of childhood brain cancer (type unspecified). However, this report gave no indication of level, duration, or frequency of exposure to diazinon (or to other insecticides) (Davis et al. 1993). Another case-control study suggested a positive association between an increased incidence of non-Hodgkin's lymphoma in farmers as compared to nonfarmers. The report attributed the increased incidence of lymphomas to handling of organophosphorus insecticides, including diazinon (Cantor et al. 1992). A third case-control study suggested an association between an increased incidence of multiple myeloma and exposure to high concentrations of insecticides, including diazinon. Actual exposure to diazinon was reported in 2 (0.3%) of the cases and 5 (0.3%) of the controls (Morris et al. 1986).

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

3.2.2 Oral Exposure

3.2.2.1 Death

In humans and animals, acute-duration oral exposure to high doses of diazinon induces cholinergic signs and symptoms. With sufficiently high doses of diazinon, extensive edema and hemorrhage in tissues and organs, as well as severe respiratory distress in the victims, have been reported. On some occasions, the respiratory effects progressed to respiratory failure and death preceded by coma. Treatment of test animals with anticholinesterase antagonists such as atropine and pralidoxime (2-PAM) significantly reduced the acute lethality of diazinon in rats, indicating that acute diazinon lethality is primarily attributable to AChE inhibition (Harris et al. 1969).

A summary of autopsy findings of 76 cases of acute diazinon poisoning described cholinergic signs that included: congested, swollen, edematous brain with prominent dural and surface vasculature; livid, congested face; cyanosis; soft flabby heart with conspicuous vasculature on the pericardium and epicardium; cloudy swelling and hyperemia (upon histopathological examination); occasional and scattered petechial and ecchymotic hemorrhage; and occasional brain or spinal hemorrhage. In addition, the victims died with congested respiratory tract, sweating and frothing at the mouth, pulmonary edema and hyperemia, hypostatic congestion, and pneumonia. Generally, the cause of death was respiratory failure and, occasionally, cardiac arrest (Limaye 1966). Other reports of human deaths from diazinon exposure include descriptions of petechial hemorrhages throughout the stomach and gastric mucosa in a diazinon-poisoned 54-year-old female suicide victim who had ingested an estimated 293 mg/kg diazinon (Poklis et al. 1980). Accidental ingestion of an insecticide mixture containing diazinon, parathion, and chlordane resulted in the death of an 8-year-old girl from cardiac and respiratory arrest (DePalma et al. 1970). The estimated dose of diazinon in this case was 20 mg/kg. The toxicity in this case may have been related to the additive effects of diazinon and parathion and/or a possible interaction with chlordane.

The diazinon dose that causes death of experimental animals depends on the form of the test compound (pure, technical, or formulated preparations) as well as on the animal species, sex, age, and other modifying factors such as diet. It is likely that earlier formulations were more toxic to experimental animals than current ones due to the formation of toxic breakdown products (e.g., sulfotepp) in unstabilized diazinon (Hayes 1982). This section summarizes lethality in animals exposed to technical-grade diazinon.

Single-dose oral (gavage) studies in rats identify lethality at dose levels ranging from approximately 75 to 600 mg (Boyd and Carsky 1969; Boyd et al. 1969; Chow and Richter 1994; Enan et al. 1982; Gaines 1960, 1969; Harris et al. 1969). Strain-specific differences in sensitivity to the lethal effects of diazinon are apparent. For example, acute oral LD_{50} values of 108 and 76 mg/kg were reported for male and female Sherman rats, respectively, whereas LD_{50} values of 415 and 466 mg/kg were noted in separate studies of male Wistar rats (Boyd and Carsky 1969; Boyd et al. 1969). A single 600 mg/kg oral dose of diazinon MG87% (88% purity; 528 mg diazinon/kg) to Sprague-Dawley rats resulted in 2/15 and 1/15 deaths in males and females, respectively (Chow and Richter 1994).

Death was noted in 6 of 8 pregnant New Zealand rabbits administered diazinon orally at a dose level of 30 mg/kg/day on gestation days 5–15 (Robens 1969). In a similar rabbit study, a dose level of 100 mg/kg/day on gestation days 6–16 resulted in 9/22 deaths (Harris and Holson 1981). No deaths were reported in pregnant CD-1 rats receiving 10, 20, or 100 mg/kg/day diazinon during gestation days 6–15 (Infurna and Arthur 1985).

Intermediate-duration oral administration of 10 or 20 mg/kg/day diazinon dissolved in corn oil in gelatin capsules for 8 months to Beagle dogs (3/sex/group) resulted in mortality (1/3 of each sex at the 20 mg/kg dose level). Toxic signs, which were not consistent in all the dogs at a given dose, did not show a dose-response relationship. Generally, female dogs were less sensitive to diazinon toxicity than male dogs (Earl et al. 1971). Daily oral administration of diazinon capsules to Hormel-Hanford miniature swine (3/sex) at a dose of 10 mg/kg/day resulted in the deaths of 3/3 males and 2/3 females between treatment days 13 and 38 of a scheduled 8-month treatment period; no deaths were observed at dose levels of 1.25, 2.5, or 5.0 mg/kg/day (Earl et al. 1971).

No deaths were reported in male or female Sprague-Dawley rats receiving up to 183.2 mg/kg/day diazinon in feed for 6 weeks or up to 212 mg/kg/day for 13 weeks (Singh 1988) or in Beagle dogs (4/sex/group) receiving up to 15.99 mg/kg/day diazinon from feed for 4 weeks or up to 11.6 mg/kg/day diazinon for 13 weeks (Barnes 1988; EPA 2000a). Survival rates were similar to controls in Sprague-Dawley rats receiving up to 12 mg/kg/day diazinon from feed for 98 weeks (Kirchner et al. 1991). Daily doses as high as 8–9 mg/kg were not lethal to male and female Beagle dogs receiving diazinon in the diet for 52 weeks (Rudzki et al. 1991).

The LD_{50} values and doses associated with death in each species and duration category are shown in Table 3-2 and plotted in Figure 3-2.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Human	once (IN)				293 F (death)	Poklis et al. 1980	
2	Rat (Wistar)	once (GO)				466 M (LD50)	Boyd and Carsky 1969	Diazinon (91.4% purity); dose adjustment for purity uncertain.
3	Rat (Wistar albino)	once (GO)				415 M (LD50)	Boyd et al. 1969	
4	Rat (Sprague-Dawley)	once (GO)				600 (2/15 males and 1/15 females died)	Chow and Richter 1994	Diazinon MG87% (D*Z*N, 88% purity); doses not adjusted for purity.
5	Rat (white)	once (GO)				300 M (LD50)	Enan et al. 1982	Diazinon (97.1% purity).
6	Rat (Sherman)	once (GO)				108 M (LD50) 76[b] F (LD50)	Gaines 1960	Technical grade diazinon (purity not specified).
7	Rat (Sherman)	once (GO)				250[b] M (LD50) 285 F (LD50)	Gaines 1969	Technical grade diazinon (purity not specified).

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
8	Rat (albino)	once (GO)				294 F (LD50)	Harris et al. 1969	Diazinon (91.9% purity).
9	Rabbit (New Zealand)	Gd 6-18 1 x/d (G)				100 F (9/22 died)	Harris and Holson 1981	Diazinon (89.2% purity) in epoxidized soybean oil; doses apparently not adjusted for purity.
10	Rabbit (New Zealand)	Gd 5-15 1 x/d (C)				30 F (6/8 died)	Robens 1969	Diazinon (technical grade, purity unspecified).
Systemic								
11	Human	once (IN)	Resp			240[b] M (tachypnea, cyanosis)	Klemmer et al. 1978	
						509 F (tachypnea, cyanosis)		
			Cardio			240[b] M (bradycardia, tachycardia)		
						509 F (bradycardia, tachycardia)		
			Hemato	240[b] M				
				509 F				
			Metab			240[b] M (metabolic acidosis)		
						509 F (metabolic acidosis)		

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
12	Human	once (IN)	Resp			293 F (heavily congested lungs)	Poklis et al. 1980	
			Gastro			293 F (petechial hemorrhages throughout the stomach and gastric mucosa)		
13	Rat (Sprague-Dawley)	once (GO)	Hemato	600			Chow and Richter 1994	Diazinon MG87% (D*Z*N, 88% purity); doses not adjusted for purity.
			Ocular		600 (chromodacryorrhea)			
			Bd Wt	150[b] M 600 F		300 M (25% decrease in weight gain)		
14	Rat (Wistar)	7 d ad lib (F)	Bd Wt	0.21			Davies and Holub 1980b	Diazinon (99.2% purity).
15	Rat (CD-1)	Gd 6-15 1 x/d (G)	Bd Wt	20 F	100 F (5.5-9.6% decrease in maternal weight, 26-30% decrease in feed consumption)		Infurna and Arthur 1985	Diazinon technical (purity unspecified).
16	Rat (Sprague-Dawley)	once (GW)	Hemato		4.4 M (reduced platelet count, altered coagulation factor activities)		Lox 1983	Diazinon (87.6% purity) dose apparently not adjusted for purity.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
17	Rat (Sprague-Dawley)	14 d ad lib (W)	Hemato		52 F (reduced hematocrit, altered clotting factor activities)		Lox 1987	Diazinon (purity not specified).
			Bd Wt	52 F				
18	Rat (Sprague-Dawley)	once (G)	Hepatic		300 (reduced hepatic cytochrome P-450, aniline hydroxylase, aminopyrine N-demethylase)		Mihara et al. 1981	
19	Rabbit (New Zealand)	Gd 6-18 1 x/d (G)	Resp	100 F			Harris and Holson 1981	Diazinon (89.2% purity) in epoxidized soybean oil; doses apparently not adjusted for purity.
			Cardio	100 F				
			Gastro	25 F		100 F (7/9 stomach mucosal hemorrhage, congestion and erosion)		
			Hepatic	100 F				
			Renal	100 F				
			Bd Wt	100 F				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
20	Human	once (IN)				240[b] M (stupor, profuse diaphoresis, coma)	Klemmer et al. 1978	
						509 F (stupor, profuse diaphoresis, coma)		
21	Human	once (IN)				293 F (petechial hemorrhages throughout the brain)	Poklis et al. 1980	
22	Rat (Sprague-Dawley)	once (GO)		2.5		150 (82% decrease in erythrocyte AChE, ataxia, alterations in functional observation battery tests 9-11 hrs post-dosing)	Chow and Richter 1994	Diazinon MG87% (D*Z*N, 88% purity); doses not adjusted for purity.
23	Rat (Wistar)	12 d ad lib (F)		0.6[c] F	1 F (22% RBC AChE inhibition)		Davies and Holub 1980a	Diazinon (99.2% purity); effects were noted at treatment day 12 of a 92-day oral study.
24	Rat (Wistar)	7 d ad lib (F)		0.21			Davies and Holub 1980b	Diazinon (99.2% purity).

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
25	Rat (Sprague-Dawley)	once (GO)			2.5 F (40% RBC AChE inhibition)	300 M (clinical signs of neurotoxicity)	EPA 2000a	Diazinon MG87% (D*Z*N, 88% purity); adjustment for purity uncertain.
26	Rat (Sprague-Dawley)	once (GO)		2.5 F	25 F (35% RBC and brain AChE inhibition)		EPA 2000a	Diazinon MG87%; adjustment for purity uncertain.
27	Rat (albino)	once (GO)				235 F (78% brain AChE inhibition)	Harris et al. 1969	Diazinon (91.9% purity).
28	Rat (Long- Evans)	once (GO)		50 M	75 M (35% brain AChE inhibition)		Moser et al. 2005	Diazinon (99.3% purity).
29	Rat (Sprague-Dawley)	once (GO)			15 M (30% RBC AChE inhibition)	60 M (>60% RBC AChE inhibition)	Timchalk et al. 2005	Diazinon (98.5% purity).
30	Hamster (Golden Syrian)	Gd 6, 7 and/or 8 1 x/d (GO)			0.125 F (diarrhea, salivation, incoordination)		Robens 1969	Diazinon (technical grade, purity unspecified).
31	Rabbit (New Zealand)	Gd 6-18 1 x/d (G)		25 F		100 F (tremors, convulsion)	Harris and Holson 1981	Diazinon (89.2% purity) in epoxidized soybean oil; doses apparently not adjusted for purity.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
32	Rabbit (New Zealand)	Gd 5-15 1 x/d (C)		7 F		30 F (ataxia)	Robens 1969	Diazinon (technical grade, purity unspecified).
Reproductive								
33	Rat (CD-1)	Gd 6-15 1 x/d (G)		100 F			Infurna and Arthur 1985	Diazinon technical (purity unspecified).
34	Rabbit (New Zealand)	Gd 6-18 1 x/d (G)		100 F			Harris and Holson 1981	Diazinon (89.2% purity) in epoxidized soybean oil; doses apparently not adjusted for purity.
Developmental								
35	Rat (CD-1)	Gd 6-15 1 x/d (G)		20 F		100 F (increased incidence of rudimentary ribs at T-14 in fetuses)	Infurna and Arthur 1985	Diazinon technical (purity unspecified).
36	Hamster (Golden Syrian)	Gd 6, 7 and/or 8 1 x/d (GO)		0.25 F			Robens 1969	Diazinon (technical grade, purity unspecified).
37	Rabbit (New Zealand)	Gd 6-18 1 x/d (G)		100 F			Harris and Holson 1981	Diazinon (89.2% purity) in epoxidized soybean oil; doses apparently not adjusted for purity.
38	Rabbit (New Zealand)	Gd 5-15 1 x/d (C)		30 F			Robens 1969	Diazinon (technical grade, purity unspecified).

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Death								
39	Dog (Beagle)	8 mo 1 x/d (C)				10 (3/3 males and 2/3 females died)	Earl et al. 1971	Technical grade diazinon (purity not specified).
40	Pig (Hormel-Hanford)	8 mo 1 x/d (C)				10 (3/3 males and 2/3 females died)	Earl et al. 1971	Technical grade diazinon (purity not specified).
Systemic								
41	Human	28-31 d (C)	Hemato	0.03 M			EPA 2001	Diazinon (99.5% purity).
42	Rat (Wistar)	7-28 wk 2 x/wk (G)	Hepatic		0.5 M (lipid vacuolation)		Anthony et al. 1986	Diazinon (87% purity); dose apparently not adjusted for purity.
			Bd Wt		0.5 M (10% reduction in body weight gain)			
43	Rat (Wistar)	92 d ad lib (F)	Bd Wt	1.2 F			Davies and Holub 1980a	Diazinon (99.2% purity).
44	Rat (Wistar)	42 d ad lib (F)	Bd Wt	0.4 F			Davies and Holub 1980a	Diazinon (99.2% purity).
45	Rat (Wistar)	35 d ad lib (F)	Bd Wt	0.2 F			Davies and Holub 1980a	Diazinon (99.2% purity).

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
46	Rat (Wistar)	30 d ad lib (F)	Bd Wt	2.86			Davies and Holub 1980b	Diazinon (99.2% purity).
47	Rat (white)	4 wk ad lib (F)	Hepatic		30 M (reduced serum beta-lipoproteins, increased ALT, AST, GGT, LDH)		Enan et al. 1982	Diazinon (97.1% purity).
48	Rat (Sprague-Dawley)	90 d (F)	Bd Wt	18 M	180 M (20% reduced body weight gain)		EPA 1996	Diazinon (D*Z*N* MG87%, purity 88%); apparently not adjusted for purity.
49	Rat (Sprague-Dawley)	28 d (F)	Bd Wt	23		213 (muscle fasciculations in forefoot; 26 and 39% decreased body weight gain in males and females, respectively)	EPA 1996	Diazinon (D*Z*N* MG87%; purity 88%); dose adjustment for purity uncertain.
50	Rat (Wistar)	7 wk 1x/d (GO)	Hepatic		10 M (40% increased serum liver enzymes, hepatocellular mitochondrial swelling and breaking up of cristae)		Kalender et al. 2005	Diazinon (99% purity)

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
51	Rat (Wistar)	7 wk 1x/d (GO)	Hemato			10 M (significantly altered hemoglobin; hematocrit; RBC, WBC, and thrombocyte counts, mean corpuscular volume)	Kalender et al. 2006	Diazinon (99% purity)
52	Rat (Sprague-Dawley)	6 mo ad lib (W)	Hemato	0.18 F			Lox and Davis 1983	Diazinon (92.4% purity) dose apparently not adjusted for purity.
			Hepatic	0.18 F				
			Bd Wt	0.18 F				
53	Rat (Wistar)	7 d 1x/d (GO)	Bd Wt			10 M (22% lower mean body weight)	Ogutcu et al. 2006	Diazinon (99% purity)

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
54	Rat (Sprague-Dawley)	13 wk 7 d/wk ad lib (F)	Resp	168[b] M 212 F			Singh 1988	Diazinon MG-8 (purity 87.7%); concentrations in food adjusted for purity.
			Cardio	168[b] M 212 F				
			Gastro	19 M 15[b] F	168[b] M (soft stools) 212 F (soft stools)			
			Hemato	168 M 19[b] F		212 F (decreased hemoglobin and hematocrit; increase in reticulocytes)		
			Hepatic	168 M 19[b] F	212 F (increase in relative and absolute liver weight, minimal centrolobular hepatocellular hypertrophy)			
			Renal	168[b] M 212 F				
			Endocr	168[b] M 212 F				
			Ocular	168[b] M 212 F				
			Bd Wt	168[b] M 212 F				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
55	Rat (Sprague-Dawley)	6 wk 7 d/wk ad lib (F)	Gastro	0.2[b] M 9.4 F	8.4[b] M (soft stools) 182.9 F (soft stools)		Singh 1988	Diazinon MG-8 (purity 87.7%); concentrations in food adjusted for purity.
			Bd Wt	8.4	150.8 M (15% decrease in body weight)			
56	Dog (Beagle)	13 wk 7 d/wk (F)	Resp	11.6			Barnes 1988	Diazinon MG-8 (purity 87.7%); concentrations in food adjusted for purity.
			Cardio	11.6				
			Gastro	11.6				
			Hemato	11.6				
			Hepatic	11.6				
			Renal	11.6				
			Endocr	5.6[b] M 11.6 F		10.9 M (atrophy of pancreatic acini)		
			Ocular	11.6				
			Bd Wt	5.9 M 0.21[b] F		10.9 M (34% decreased weight gain in males) 5.6[b] F (33% decreased weight gain in females)		

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
57	Dog (Beagle)	4 wk 7 d/wk (F)	Hemato	15.99			Barnes 1988	Diazinon MG-8 (purity 87.7%); concentrations in food adjusted for purity.
			Hepatic	15.99				
			Renal	15.99				
			Bd Wt	0.8	14.68 M (weight loss)	15.99 F (emaciation- 20% weight loss)		

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
58	Dog (Beagle)	8 mo 1 x/d (C)	Cardio	5 M[b] 20 F	10 M (no pericardial fat, cord-like heart vessels)		Earl et al. 1971	Technical grade diazinon (purity not specified).
			Gastro	5	10 M (duodenal wall thickening)	20 (duodenal and stomach ruptures)		
			Hemato	10 F		10 M[b] (peripheral anemia; bone marrow hypocellularity, increased myeloid element content, reticulocytopenia)		
						20 F (peripheral anemia; bone marrow hypocellularity, increased myeloid element content, reticulocytopenia)		
			Hepatic	2.5	5 (markedly elevated serum AST and OCT)	10 M (yellow, fatty liver; parenchymal atrophy, hepatocyte dissociation; moderate cirrhosis focal necrosis, fibrous infiltration elevated serum LDH)		
			Renal	5 M[b] 10 F		10 M (localized chronic nephritis, tubular atrophy, glomeruli necrosis, fibrous infiltration, elevated serum LDH)		
			Endocr	5		10 M (pancreatic atrophy and interstitial fibrosis)		
			Bd Wt	5 M[b] 10 F	10 M[b] (significant weight loss) 20 F (significant weight loss)			

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
59	Pig (Hormel-Hanford)	8 mo 1 x/d (C)	Gastro	1.25	2.5	(edema and serosal seepage in the ileum)	10	(jejunal edema, localized mucosal erosion into intestinal muscle layers with marked serosal seepage; duodenal ulceration)	Earl et al. 1971	Technical grade diazinon (purity not specified).
			Hemato	2.5			5	(occasional transient peripheal anemia, reticulocytopenia, bone marrow hypocellulartiy, increased myeloid element content)		
			Hepatic		1.25	(slight inflammation, occasional lobular congestion)	5			
							2.5	(interlobular connective tissue thickening, degenerative hepatocytes, hepatic hemorrhage)		
Immuno/ Lymphoret										
60	Rat (Sprague-Dawley)	13 wk 7 d/wk ad lib (F)		168[b] M 212 F					Singh 1988	Diazinon MG-8 (purity 87.7%); concentrations in food adjusted for purity.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
61	Dog (Beagle)	13 wk 7 d/wk (F)		11.6			Barnes 1988	Diazinon MG-8 (87.7% purity); concentrations in food adjusted for purity.
Neurological								
62	Human	28-31 d (C)		0.03 M			EPA 2001	Diazinon (99.5% purity).
63	Rat (Wistar)	42 d ad lib (F)		0.18 F[d]	0.27 F (20% RBC AChE inhibition)		Davies and Holub 1980a	Diazinon (99.2% purity).
64	Rat (Wistar)	35 d ad lib (F)		0.2 F			Davies and Holub 1980a	Diazinon (99.2% purity).
65	Rat (Wistar)	92 d ad lib (F)		0.4 F	0.8 F (40% RBC AChE inhibition)		Davies and Holub 1980a	Diazinon (99.2% purity).
66	Rat (Wistar)	30 d ad lib (F)			2.86 (58% RBC AChE inhibition)		Davies and Holub 1980b	Diazinon (99.2% purity).
67	Rat (Sprague-Dawley)	90 d (F)		0.018		1.8 F (greater than 79-86% RBC AChE inhibition)	EPA 1996	Diazinon (D*Z*N* MG87%, purity 88%); apparently not adjusted for purity.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
68	Rat (Sprague-Dawley)	28 d (F)		0.02	2.4 (38-59% RBC AChE inhibition)		EPA 1996	Diazinon (D*Z*N* MG87%; purity 88%); dose adjustment for purity uncertain.
69	Rat (Sprague-Dawley)	133 d (F)		7.63 F		41.43 F (tremors in 3/30 and 4/30 F0 and F1 parental females)	Giknis 1989	Diazinon technical (94.9% purity); dose adjustment for purity uncertain.
70	Rat (Sprague-Dawley)	42 d (F)		0.17 M 0.19 F	1.68 M (29-35% RBC AChE inhibition) 1.82 F (16-35% RBC AChE inhibition)	8.6 M (>59% RBC AChE inhibition) 9.27 F (>59% RBC AChE inhibition)	Mahkteshim-Agan 1989	Diazinon (97.2% purity); no allowance was made for purity
71	Rat (Sprague-Dawley)	6 wk 7 d/wk (F)		0.2 M	8.4[b] M (21% RBC AChE inhibition) 9.4 F (24% brain AChE inhibition)	150.8[b] M (58% decrease in brain AChE in males, 61% decrease in females) 182.9 F (61% decrease in brain AChE in females)	Singh 1988	Diazinon MG-8 (purity 87.7%); concentrations in food adjusted for purity.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
72	Rat (Sprague-Dawley)	13 wk 7 d/wk ad lib (F)		0.4	15 M (27% RBC AChE inhibition)		Singh 1988	Diazinon MG-8 (purity 87.7%); concentrations in food adjusted for purity.
73	Rat (Sprague-Dawley)	42 d (F)		0.19 M 0.2 F	1.81 M (46-55% RBC AChE inhibition)	9.08 M (>59% RBC AChE inhibition) 1.97 F (>59% RBC AChE inhibition)	Trutter 1991	Diazinon (87.4% purity); concentrations in food adjusted for purity
74	Dog (Beagle)	13 wk 7 d/wk (F)		0.021	5.9 (31% RBC and brain AChE inhibition)		Barnes 1988	Diazinon MG-8 (87.7% purity); concentrations in food adjusted for purity.
75	Dog (Beagle)	4 wk 7 d/wk (F)		0.082	14.68 (30% RBC AChE inhibition, 44% brain AChE inhibition, emesis)		Barnes 1988	Diazinon MG-8 (87.7% purity); concentrations in food adjusted for purity.
76	Dog (Beagle)	8 mo 1 x/d (C)		5	10 (fasciculation, diarrhea, emesis)		Earl et al. 1971	Technical grade diazinon (purity not specified).
77	Pig (Hormel-Hanford)	8 mo 1 x/d (C)		1.25	2.5 (emesis, diarrhea, fasciculations)		Earl et al. 1971	Technical grade diazinon (purity not specified).

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
78	Rat (albino)	65 d (GW)				1.5 M (increased sperm abnormalities, decreased fertility)	Abd El-Aziz et al. 1994	Diazinon (purity unspecified)
79	Rat (Sprague-Dawley)	133 d (F)		41.43 F			Giknis 1989	Diazinon technical (94.9% purity); dose adjustment for purity uncertain.
80	Rat (Sprague-Dawley)	60 d ad lib (F)		0.05			Green 1970	Diazinon (purity unspecified).
81	Rat (Sprague-Dawley)	13 wk 7 d/wk ad lib (F)		168[b] M 212 F			Singh 1988	Diazinon MG-8 (purity 87.7%); concentrations in food adjusted for purity.
82	Mouse (Hybrid)	Gd 1-18 1 x/d (F)			0.18 F (14% reduced maternal weight gain, 20% reduced litter size)		Spyker and Avery 1977	Diazinon technical grade (purity not specified).
83	Dog (Beagle)	13 wk 7 d/wk (F)		11.6			Barnes 1988	Diazinon MG-8 (87.7% purity); concentrations in food adjusted for purity.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
84	Dog (Beagle)	8 mo 1 x/d (C)		5 M		10 M (testicular atrophy, aspermatogenesis)	Earl et al. 1971	Technical grade diazinon (purity not specified).
Developmental								
85	Rat (Sprague-Dawley)	133 d (F)		0.77 F		7.63 F (decreased F1 pup survival)	Giknis 1989	Diazinon technical (94.9% purity); dose adjustment for purity uncertain.
86	Mouse (Hybrid)	Gd 1-18 1 x/d (F)		0.18		9 (significantly reduced early weight gain by pups, increased mortality at ppd 28)	Barnett et al. 1980	Diazinon (technical grade, purity unspecified).
87	Mouse (Hybrid)	Gd 1-18 1 x/d (F)				0.18 F (neuromuscular coordination deficits, reduced litter size, delayed contact placing and sexual maturity)	Spyker and Avery 1977	Diazinon technical grade (purity not specified).

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
88	Rat (Sprague-Dawley)	98 wk or 52 wk (F)	Resp	11			Kirchner et al. 1991	Diazinon MG-8 (87.7% purity); concentrations in food adjusted for purity.
			Cardio	11				
			Gastro	11				
			Hemato	11				
			Musc/skel	11				
			Hepatic	11				
			Renal	11				
			Endocr	11				
			Dermal	11				
			Ocular	11				
			Bd Wt	11				
			Metab	11				
89	Dog (Beagle)	52 wk (F)	Hemato	8.4			Rudzki et al. 1991	Diazinon MG-6 (87.7% purity); dose adjustment for purity uncertain.
			Bd Wt	0.015 M		4.7 M (42% depressed body weight gain)		

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
90	Rat (Sprague-Dawley)	98 wk or 52 wk (F)		11			Kirchner et al. 1991	Diazinon MG-8 (87.7% purity); concentrations in food adjusted for purity.
Neurological								
91	Rat (Sprague-Dawley)	98 wk or 52 wk (F)		0.065[e]	5.5 (22-29% RBC and brain AChE inhibition)		Kirchner et al. 1991	Diazinon MG-8 (87.7% purity); concentrations in food adjusted for purity.
92	Dog (Beagle)	52 wk (F)		0.017	4.6 (21-35% RBC AChE inhibition)		Rudzki et al. 1991	Diazinon MG-6 (87.7% purity); dose adjustment for purity uncertain.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
93	Rat (Sprague-Dawley)	98 wk or 52 wk (F)		11			Kirchner et al. 1991	Diazinon MG-8 (87.7% purity); concentrations in food adjusted for purity.

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

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c Used to derive an acute-duration oral minimal risk level (MRL) of 0.006 mg/kg/day for diazinon based on significant RBC AChE inhibition in female rats by treatment day 12 of the 92-day study. The NOAEL of 0.6 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

d Study results used to derive an intermediate-duration oral minimal risk level (MRL) of 0.002 mg/kg/day for diazinon, as described in detail in Appendix A. Benchmark dose (BMD) analysis was performed on RBC AChE activity to select a point of departure, which was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

e Used to derive a chronic-duration oral minimal risk level (MRL) of 0.0007 mg/kg/day for diazinon. The NOAEL of 0.065 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

AChE = acetylcholinesterase; ad lib = ad libitum; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; gd = gestational day; (GO) = gavage in oil; GGT = gamma-glutamyl-transferase; (GW) = gavage in water; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; (IN) = ingestion; LD50 = lethal dose, 50% kill; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; Metab = Metabolic; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; OCT = ornithine carbamyl transferase; ppd = post-parturition day; RBC = red blood cell; Resp = respiratory; x = time(s); (W) = drinking water; wk = week(s); yr = year(s)

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

Acute (≤14 days)

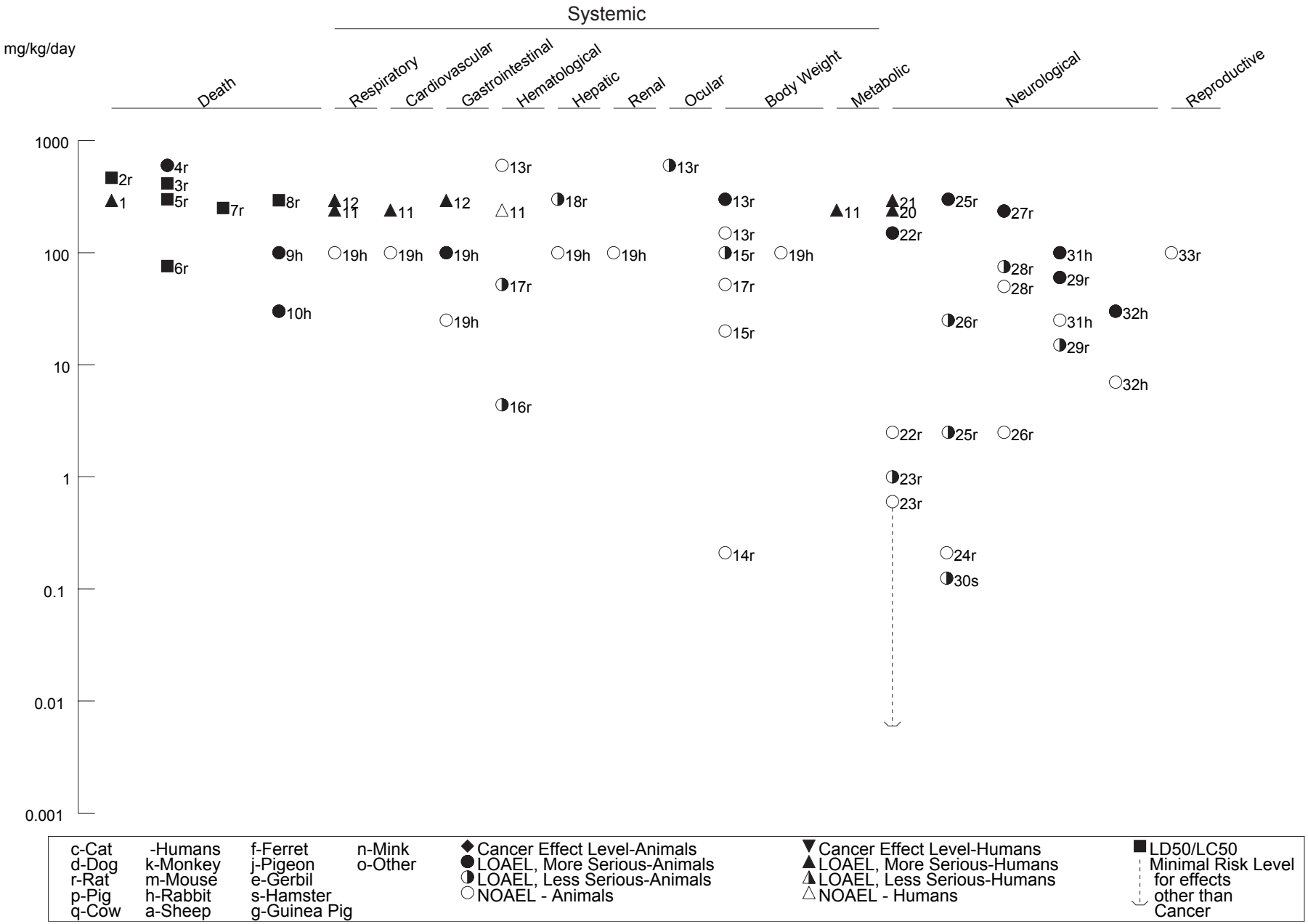


Figure 3-2 Levels of Significant Exposure to Diazinon - Oral *(Continued)*

Acute (≤14 days)

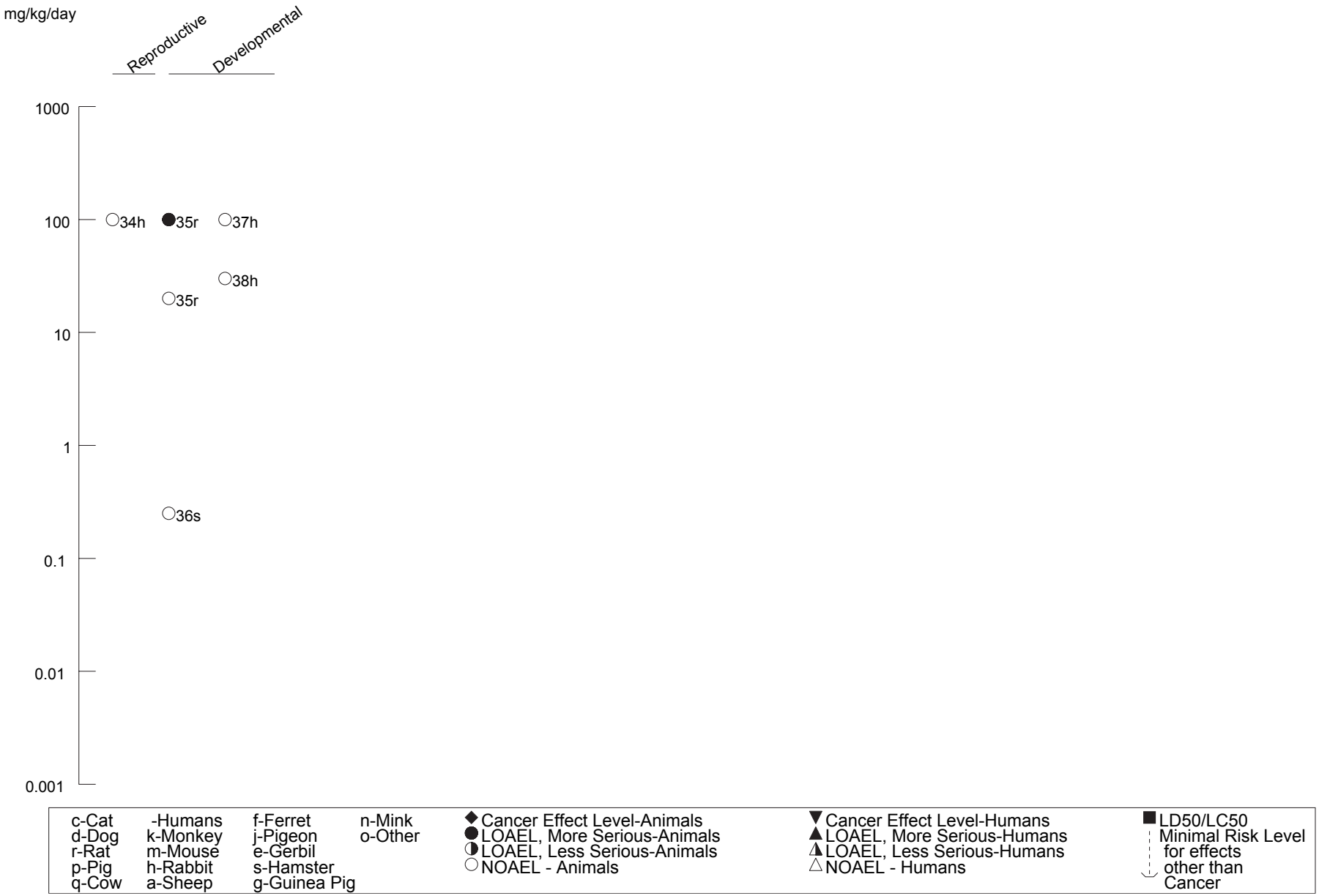


Figure 3-2 Levels of Significant Exposure to Diazinon - Oral *(Continued)*

Intermediate (15-364 days)

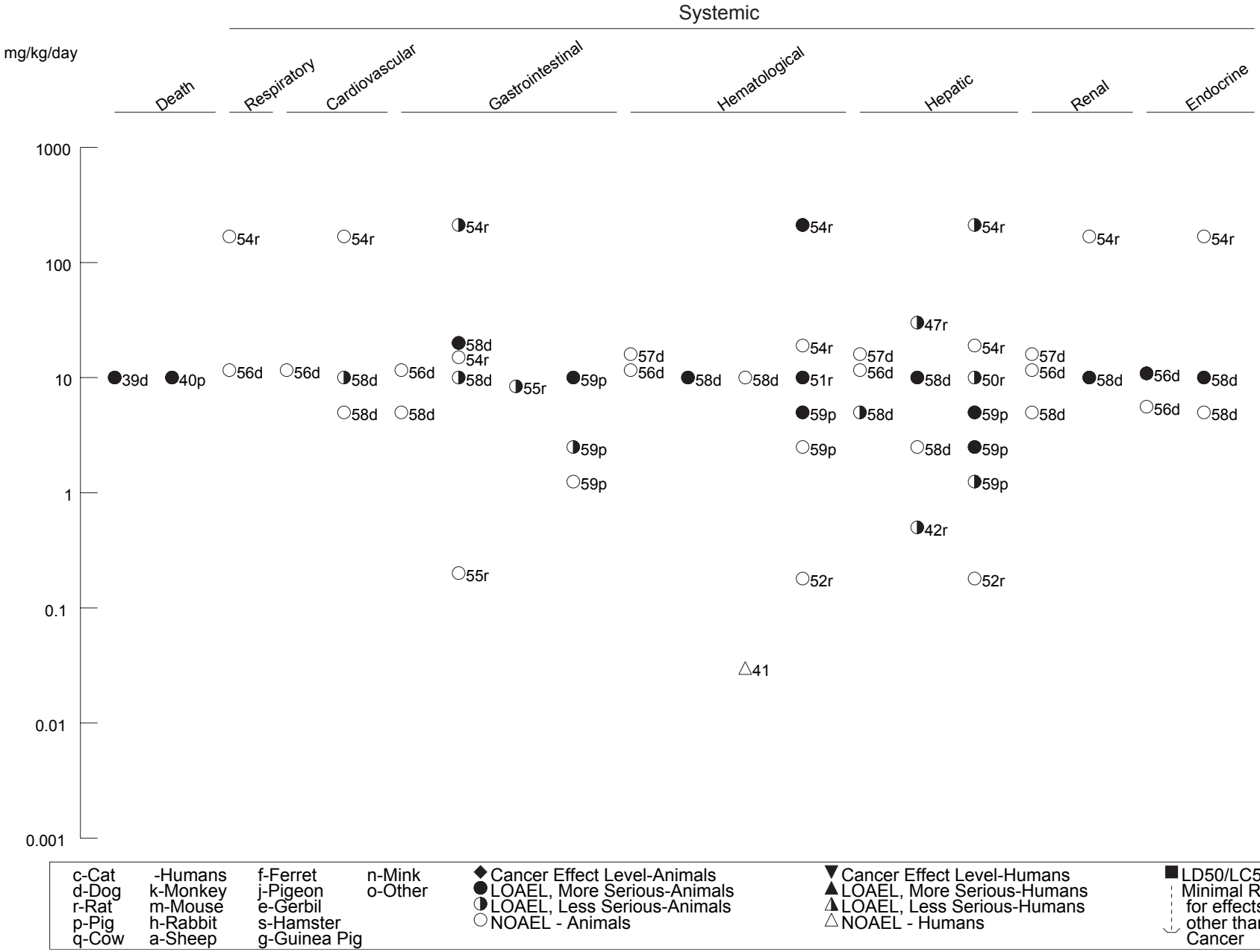


Figure 3-2 Levels of Significant Exposure to Diazinon - Oral *(Continued)*

Intermediate (15-364 days)

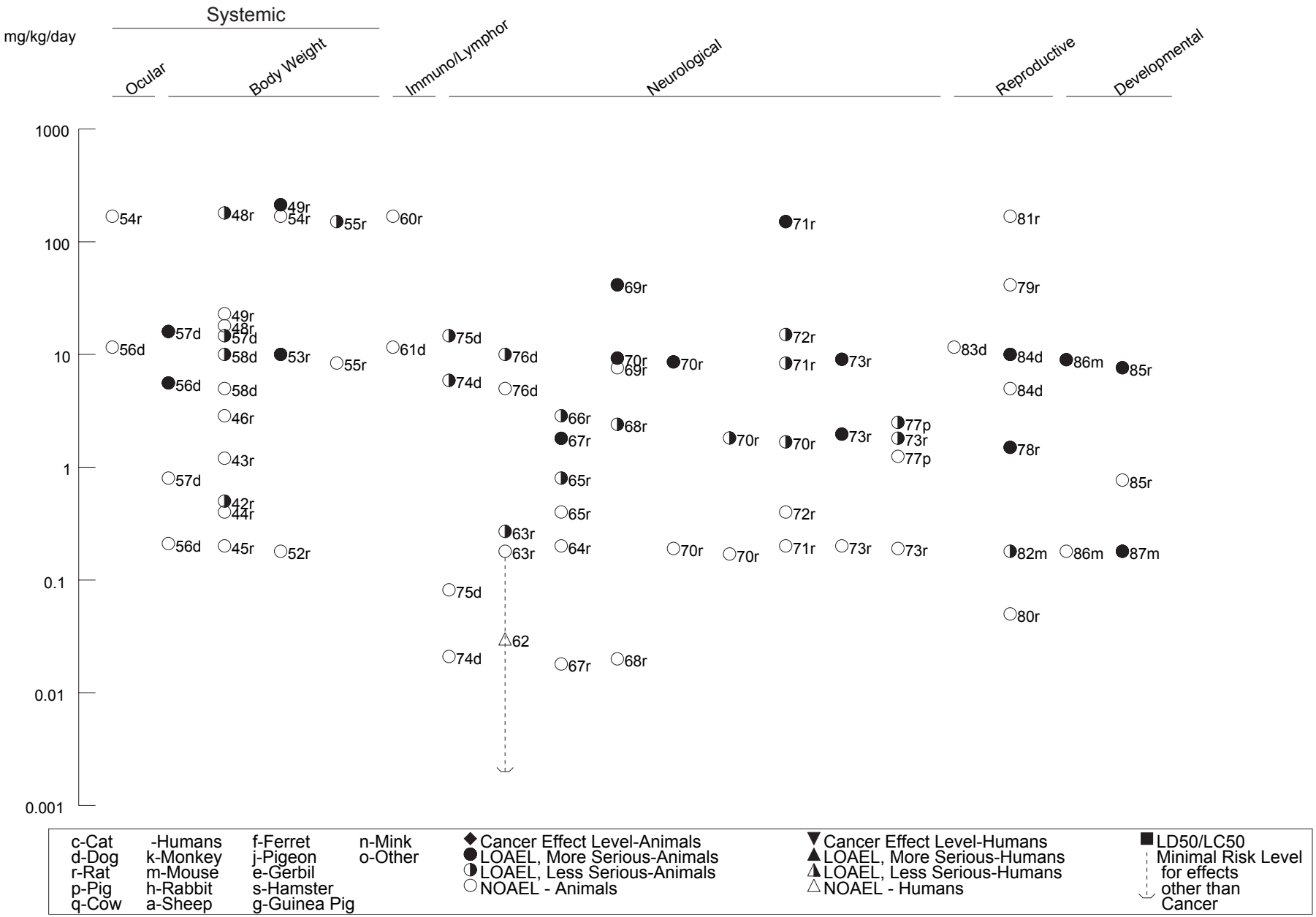
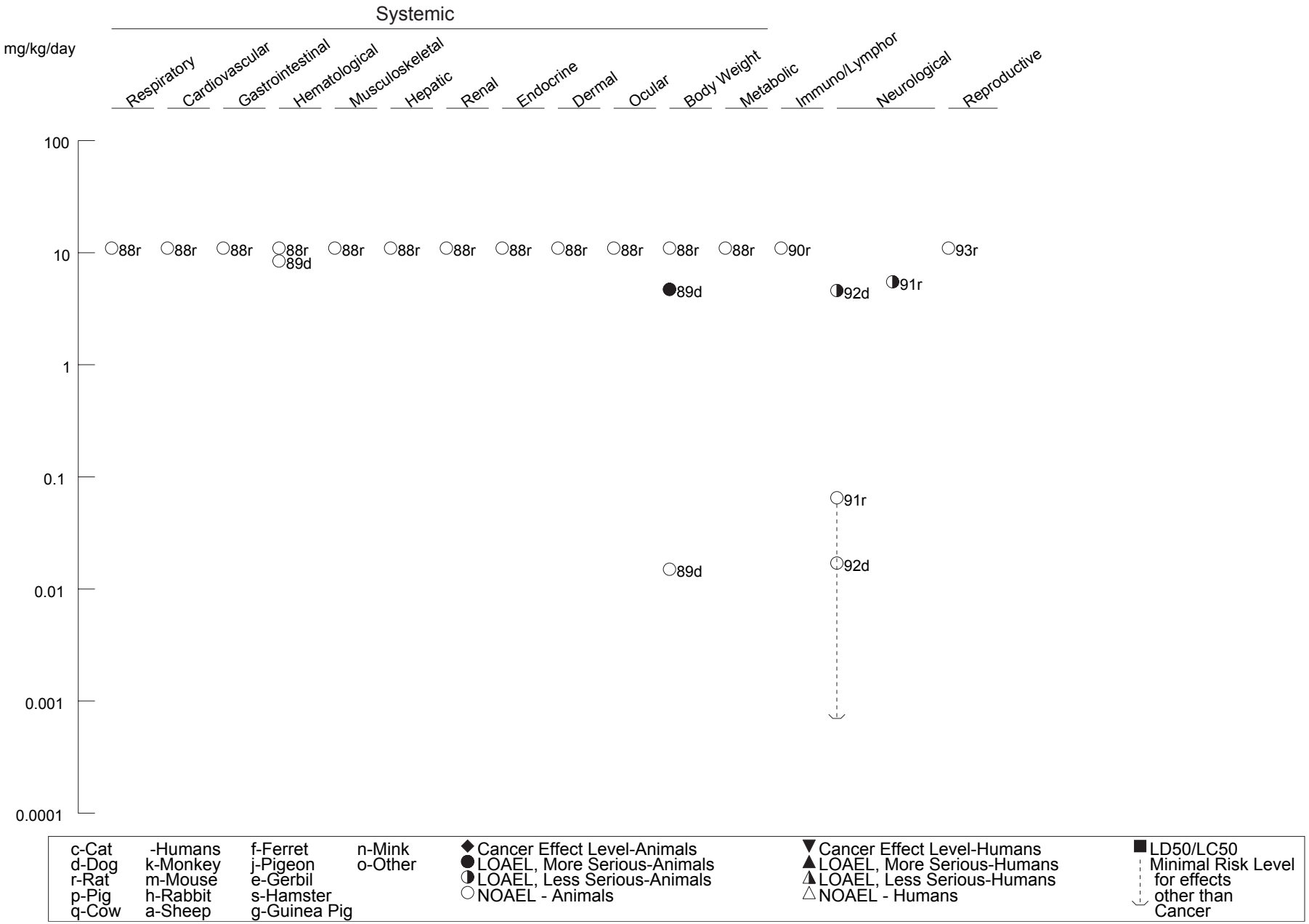


Figure 3-2 Levels of Significant Exposure to Diazinon - Oral *(Continued)*

Chronic (≤365 days)



3.2.2.2 Systemic Effects

No studies were located regarding musculoskeletal, dermal, or body weight effects in humans after oral diazinon exposure. No information was located regarding musculoskeletal or dermal effects in animals after oral exposure to diazinon. Autopsy findings in human acute diazinon poisonings and laboratory animal lethality studies, as well as findings from other human and laboratory animal nonlethal oral exposures, included respiratory impairment, cardiovascular, gastrointestinal, hematological, and endocrine (pancreas) effects. These effects were largely derived from cholinergic responses typical of high-level organophosphate poisoning.

The highest NOAEL value and all LOAEL values for systemic effects in each reliable study for each species and duration category are shown in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. Respiratory distress, a typical cholinergic sign of AChE inhibition, was reported in several human acute poisoning incidents and laboratory animal evaluations following oral diazinon exposure. In humans, acute-duration oral exposure to high doses of diazinon causes pulmonary distress with signs that include congested respiratory tract, copious airway secretions, and pulmonary edema (Balani et al. 1968; Hata et al. 1986; Kabrawala et al. 1965). An 18% incidence of pulmonary edema was found in diazinon-poisoned patients (Limaye 1966; Shankar 1967). An autopsy report of a diazinon-poisoned 54-year-old female suicide victim described heavy and congested (edematous) lungs (Poklis et al. 1980). Tachypnea and cyanosis were observed in a male who intentionally ingested 240 mg/kg diazinon and in a female who ingested 509 mg/kg (Klemmer et al. 1978). Diazinon treatment also resulted in signs of respiratory effects in laboratory animals. Single oral diazinon doses of 50–700 mg/kg to rats resulted in respiratory distress from pulmonary inflammation, vascular congestion, venous stasis, and occasional extensive pneumonitis. Death generally resulted from respiratory failure that was usually preceded by coma (Boyd and Carsky 1969). Dyspnea was observed in male Sprague-Dawley rats given a single gavage dose of 264 mg/kg diazinon and impaired respiration was observed in females receiving a dose of 528 mg/kg (Chow and Richter 1994).

No gross or histological evidence of treatment-related damage to the lungs was observed in New Zealand rabbit dams receiving up to 100 mg/kg/day diazinon during gestation days 6–18 (Harris and Holson 1981), in male or female Sprague-Dawley rats receiving up to 212 mg/kg/day diazinon from feed for 13 weeks (Singh 1988) or up to 12 mg/kg/day for 98 weeks (Kirchner et al. 1991), or in male or female Beagle dogs receiving up to 11.6 mg/kg/day diazinon for 13 weeks (Barnes 1988).

Cardiovascular Effects. Acute-duration oral, lethal human exposure to diazinon resulted in extensive congestion of the heart and blood vessels as reported in a summary of autopsy findings of 76 cases of acute diazinon poisoning which described cardiovascular signs that included: livid, congested face; soft flabby heart with conspicuous vasculature on the pericardium and epicardium; occasional and scattered petechial/ecchymotic hemorrhage; and cloudy swelling and hyperemia (upon histopathological examination) (Limaye 1966). In a case study of 25 attempted suicides by diazinon ingestion, some patients showed hypertension and peripheral circulatory failure (Kabrawala et al. 1965). Other cardiovascular signs reported after acute oral exposure to high doses of diazinon in humans include tachycardia (Kabrawala et al. 1965; Klemmer et al. 1978; Shankar 1967), hypertension (Balani et al. 1968; Hata et al. 1986), and bradycardia (Hata et al. 1986; Klemmer et al. 1978).

One male dog given 10 mg/kg/day diazinon for 8 months exhibited an absence of pericardial fat on the heart, as well as a cord-like appearance of the heart vessels (Earl et al. 1971). Two other dogs, given 10 or 20 mg/kg/day diazinon, exhibited markedly elevated serum lactate dehydrogenase (LDH). This is a nonspecific response that may be suggestive of either cardiac or skeletal muscle damage or some other unknown pathology. Pallor was reported in male Sprague-Dawley rats receiving a single oral dose of 132 mg/kg diazinon (Chow and Richter 1994). Oral administration of 10 mg/kg/day diazinon to rats for 7 weeks resulted in significantly increased malondialdehyde levels in heart tissue and histopathologic evidence of vacuolization and swelling of mitochondria in myocardial cells (Ogutcu et al. 2006). The biological significance of these results is uncertain because the diazinon-treated rats exhibited 22% lower mean body weight than controls.

No gross or histological evidence of treatment-related damage to the heart was seen in New Zealand rabbit dams receiving up to 100 mg/kg/day diazinon during gestation days 6–18 (Harris and Holson 1981), in male or female Sprague-Dawley rats receiving up to 212 mg/kg/day diazinon in feed for 13 weeks (Singh 1988) or up to 12 mg/kg/day diazinon in feed for 98 weeks (Kirchner et al. 1991), or in male or female Beagle dogs receiving up to 11.6 mg/kg/day diazinon for 13 weeks (Barnes 1988).

Gastrointestinal Effects. A summary of autopsy findings from 76 cases of acute diazinon poisoning describes gastrointestinal signs that include: dark, blood-stained stomach contents; congested stomach mucosa with submucosal petechial hemorrhage; and occasional erosion and ulceration (Limaye 1966). Petechial hemorrhages throughout the stomach and gastric mucosa were revealed in the autopsy report of a diazinon-poisoned 54-year-old female suicide victim who had ingested an estimated 293 mg/kg

diazinon (Poklis et al. 1980). Other signs of gastrointestinal toxicity seen in humans after acute exposure to high doses of diazinon include nausea, diarrhea and vomiting (Balani et al. 1968; Klemmer et al. 1978), and abdominal pain (Balani et al. 1968). A 16-year-old female who drank an estimated 1.5 mg/kg of a diazinon formulation (Tik-20) developed pancreatitis after being treated for cholinergic manifestations. The pancreatic effects may well have been secondary to the diazinon-induced cholinergic manifestations (Dagli et al. 1981). Acute pancreatitis was also found in two children poisoned with diazinon (Weizman and Sofer 1992).

In male albino Wistar rats exposed to acute lethal doses of diazinon, lamina propria of the small intestine were congested, and occasional small areas of hemorrhage and necrosis at the mouth of gastric glands were observed. The digestive tract was dehydrated with small increases in organ wet weight except for the cecum, whose wet weight declined approximately 32%. Other effects included pyloric stomach ulceration and inflammation of the small intestine and cecum (Boyd and Carsky 1969). Similar effects were seen in an intermediate exposure of Beagle dogs given diazinon orally for 8 months. Marked edematous thickening of the intestinal wall was observed in 5/6 dogs at the lethal 20 mg/kg/day dose with one developing a duodenal rupture and subsequent peritonitis, and another rupture of the pyloric portion of the stomach. At the 10 mg/kg/day dose, the duodenal wall thickening was observed only in the solitary male dog that exhibited weight loss and other gross pathological changes. Elevated serum amylase levels were also found in dogs of both sexes at the 10 mg/kg/day dose, but apparently did not correlate with observable pancreatic pathology with the exception of one male dog. Either congestion or hemorrhage (or both) of the small intestines and colon was present in varying degrees among dogs receiving 5–100 mg/kg/day diazinon for various time periods in a preliminary dose-range study. Apparently, many of the effects described were not found uniformly in all of the dogs at a given dose, and a clear dose-response relationship was not always present (Earl et al. 1971). Treatment of Hormel-Hanford miniature pigs with daily diazinon doses of 1.25–10 mg/kg/day for 8 months resulted in injury to the gastrointestinal tract. At 10 mg/kg/day, 4/5 pigs which died had edematous thickening of the walls of the jejunum, 3/5 had ulcer formation in the duodenum, and one had localized mucosal erosion into the muscular layer with serosal seepage throughout the intestines. One pig at each of the 5.0 and 2.5 mg/kg/day dose levels displayed edema of the jejunum; serosal seepage of the ileum was noted at the lower dose. Histopathologically, slight thickening of the serosa, occasional focal hyperemia, and outer muscle hemorrhaging were observed in the intestines of swine exposed to 10 or 5 mg/kg/day diazinon. Abdominal ascites that clotted on exposure to air was reported without further description for one pig exposed to 2.5 mg/kg/day. This animal also suffered intestinal edema and serosal seepage, liver toxicity, and death on day 141 (Earl et al. 1971).

Stomach mucosal hemorrhage, congestion, and erosion were observed in 7/9 New Zealand rabbit dams that died while receiving 100 mg/kg/day diazinon during gestation days 6–18 (Harris and Holson 1981). No signs of gastrointestinal toxicity were seen in dams treated at 7 or 25 mg/kg/day. Diarrhea was observed in male Sprague-Dawley rats receiving a single oral dose of 528 mg/kg diazinon, but not in females receiving the same dose (Chow and Richter 1994). Soft stools were observed in male Sprague-Dawley rats receiving 8.4 mg/kg/day diazinon from feed for 6 weeks and in females receiving 183.2 mg/kg/day (Singh 1988), as well as males receiving 168 mg/kg/day diazinon from feed for 13 weeks and in females receiving 212 mg/kg/day (Singh 1988). Emesis was reported in male and female Beagle dogs receiving 14.68 mg/kg/day diazinon from feed for 4 weeks (EPA 2000a). Emesis, bloody feces, and diarrhea were observed in Beagle dogs receiving up to 11.6 mg/kg/day diazinon from feed for 13 weeks (Barnes 1988). These signs were not dose-related and were considered by the authors to be unrelated to treatment.

No histological evidence of treatment-related damage to gastrointestinal tissues was found in Sprague-Dawley rats receiving up to 12 mg/kg/day diazinon for 98 weeks (Kirchner et al. 1991), or up to 212 mg/kg/day for 13 weeks (Singh 1988). Similar results were reported in Beagle dogs receiving up to 11.6 mg/kg/day diazinon over a 13-week period (Barnes 1988).

Hematological Effects. A report on five individuals (three males, two females) who intentionally ingested 60–180 mL of 25% diazinon solution (estimated to deliver a dose of 240–400 mg/kg for males and 509–986 mg/kg for females) found that leucocyte counts (3,700, 95% polymorphonuclear), hemoglobin (16.3 g), and hematocrit (47) were all within normal ranges (Klemmer et al. 1978).

Diazinon-induced hematological effects have been reported in several animal studies. The hematological effects of a single oral dose of 4.4 mg/kg diazinon were studied in Sprague-Dawley rats 2 hours after treatment. Although diazinon exposure did not significantly alter hematocrit or factor VII activity, platelet count was significantly ($p<0.05$) reduced when compared with pre-exposure values ($694x10^3/mm^3$ as compared to $856x10^3/mm^3$). Similarly, small (6–14%) but significant ($p<0.05$) changes were observed in activities of the remaining clotting factors; fibrinogen activity was reduced, while prothrombin, partial thromboplastin, factor II, factor V, and factor X activities were increased. Since fibrinogen and factors II, V, VII, and X are synthesized in the liver, the associated alterations may reflect hepatic effects of diazinon exposure. The data indicate an overall diazinon-induced condition of hyper-coagulability that, considered together with observations from other studies of various haemorrhagia, may

suggest that diazinon might affect hemostasis in general (Lox 1983). Other rats received 52 mg/kg/day diazinon from drinking water for 14 days and were monitored for hematocrit and platelet count, and various clotting factor times (prothrombin, partial thromboplastin, fibrinogen, and factors II, V, VII, X, and XII). Immediately after treatment, increased times for prothrombin, partial thromboplastin, and fibrinogen suggest an overall state of hypocoagulability, despite no consistent pattern for the other factors and parameters (decreased for VII and XII, no changes for II, V, VII, and X, or in hematocrit and platelet count). One week after treatment, partial thromboplastin time was shortened (indicating intrinsic pathway activation), as were the clotting times for factors VIII, X, and XII, although that for II was lengthened. Overall, this suggests a hypercoagulability of the intrinsic pathway. Also, hematocrit was decreased. These alterations may reflect a time-course in hepatic damage (at least for II, VII, X, and fibrinogen which are of liver origin) (Lox 1987). A group of 24 rats receiving approximately 0.18 mg/kg/day diazinon from drinking water for 6 months showed no changes compared with controls in the clotting activities associated with prothrombin, partial thromboplastin, fibrinogen, or the coagulation factors II, V, VII, and X (Lox and Davis 1983). Significantly ($p<0.01$) decreased hematocrit, hemoglobin, and RBC and thrombocyte counts, and increased white blood cell (WBC) count and mean corpuscular volume were observed in rats orally administered 10 mg/kg/day diazinon for 7 weeks (Kalender et al. 2006). One of six dogs treated with 20 mg/kg/day diazinon exhibited marked reductions in peripheral red blood cells, hematocrit, and hemoglobin. All six dogs displayed greatly elevated myeloid/erythroid (M/E) bone marrow ratios (114–183/1 as opposed to 1.1–1.9/1 for controls) with slight to moderate bone marrow hypocellularity, and a pronounced reticulocytopenia in two dogs (one male, one female) (Earl et al. 1971). Three of six Hormel-Hanford miniature pigs orally administered 5.0 mg/kg/day diazinon showed a transient drop in red blood cells, hematocrit, and hemoglobin content, but no indication of peripheral anemia. No peripheral anemia was present in any of five pigs in the 10 mg/kg/day group, but all the pigs exhibited reticulocytopenia, with three displaying elevated M/E ratios (Earl et al. 1971).

Hematological parameters were normal in Sprague-Dawley rats (10–15/sex/group) receiving a single oral gavage dose of up to 528 mg/kg diazinon and examined 14 days later (Chow and Richter 1994). Decreased hemoglobin and hematocrit along with an increase in reticulocytes were observed in female Sprague-Dawley rats receiving 212 mg/kg/day diazinon from feed for 13 weeks. Hematological parameters were normal in female rats receiving up to 19 mg/kg/day and in males receiving up to 168 mg/kg/day (Singh 1988). No changes in hematological parameters were observed in Beagle dogs receiving up to 11.6 mg/kg/day diazinon from feed for 13 weeks (Barnes 1988) or up to 9 mg/kg/day for 52 weeks (Rudzki et al. 1991), or in Sprague-Dawley rats receiving up to 12 mg/kg/day for 98 weeks (Kirchner et al. 1991).

Hepatic Effects. A summary of autopsy reports from 76 human diazinon poisonings includes findings of congested liver (Limaye 1966).

In laboratory animals, single oral doses of 300 mg/kg diazinon given to male and female Sprague-Dawley rats were followed by significant ($p<0.001–0.05$) reductions in hepatic microsomal cytochrome P-450 content and aniline hydroxylase and aminopyrine N-demethylase activities, especially during the first 24 hours. These effects largely disappeared within 72 hours to 2 weeks, with values often exceeding those of controls. No significant changes in mitochondrial respiratory function (respiratory control ratio, ADP/O ratio, and ATPase activity) were observed (Mihara et al. 1981). Oral administration of 30 mg/kg/day diazinon for 4 weeks to white male rats reduced serum beta-lipoprotein, alanine amino-transferase, aspartate aminotransferase, and gamma-glutamyl transferase. Although elevated levels of these transaminases are generally associated with liver pathology, the toxicological implications of the significant reduction (13–67%) of these liver enzymes and its relevance to diazinon poisoning are unclear (Enan et al. 1982). In another rat study, normal lobular architecture was maintained in the livers, but small lipid droplets were observed in some hepatocytes after 7 weeks. In this study, male Wistar rats were treated with oral doses of 0.5 mg/kg twice a week for 28 weeks. Lipid accumulation became progressively more severe from 14 to over 28 weeks, but no cellular necrosis was observed (at least after 14 weeks). This lipid accumulation could result from disturbed metabolism in the hepatocellular rough endoplasmic reticulum, increased lipid mobilization from peripheral tissue, or impaired lipoprotein release from liver cells. Electron microscopic examination revealed fat droplets near mitochondria, with abundant rough and smooth endoplasmic reticulum, mitochondria, and glycogen present in liver cells from both treated and control rats. No changes were observed in hepatocyte nuclei or nucleoli. But in another study, groups of rats exposed to approximately 0.18 mg/kg/day diazinon in the drinking water for 6 months exhibited no adverse effects on the liver as determined by histopathological examination (Lox and Davis 1983). The autopsy of a male Beagle dog that died from exposure to 10 mg/kg/day diazinon for 8 months revealed fatty liver, markedly elevated serum aspartate aminotransferase, serum lactate dehydrogenase, and ornithine carbamyl transferase, parenchymal atrophy, and hepatocyte dissociation (Earl et al. 1971). Female dogs treated with 20 mg/kg/day diazinon showed moderate cirrhosis, focal necrosis, fibrous infiltration, and hepatocyte dissociation. In another study, hepatic effects noted in pigs treated with 1.25 mg/kg/day diazinon for 8 months included slight inflammation and occasional lobular congestion with degenerative hepatocytes (Earl et al. 1971). Animals treated with a daily dose of 2.5 mg/kg exhibited interlobular connective tissue thickening and lobular congestion. In addition to the noted hepatic effects, all livers from swine exposed to 10 mg/kg/day were very firm to the touch and hard

to cut, and one liver from a pig treated with 5 mg/kg/day diazinon was described as “friable” and very gritty, with focal subscapular hemorrhages.

An increase in relative and absolute liver weight was observed in female Sprague-Dawley rats receiving 212 mg/kg/day diazinon from feed for 13 weeks (Singh 1988). This was accompanied by histological evidence of minimal centrilobular hepatocellular hypertrophy. Kalender et al. (2005) noted serum biochemical and hepatocellular structural changes in male Wistar rats administered diazinon by gavage at a dose of 10 mg/kg/day for 7 weeks. The observed effects included significantly ($p<0.01$) increased hepatic enzyme activity (ALP, ALB, AST), total protein, and albumin levels, increased total cholesterol and decreased low density lipoprotein cholesterol and triglycerides, and histopathologic evidence of pronounced mitochondrial swelling, structural changes in mitochondrial cristae, swelling of endoplasmic reticulum, and changes in the density of nuclear chromatin.

No gross or histological evidence of treatment-related damage to the liver after oral exposure to diazinon was observed in Sprague-Dawley rats receiving up to 12 mg/kg/day diazinon for 98 weeks (Kirchner et al. 1991), in New Zealand rabbit dams receiving up to 100 mg/kg/day diazinon during gestation days 6–18 (Harris and Holson 1981), or in Beagle dogs (4/sex/group) receiving up to 11.6 mg/kg/day diazinon for 13 weeks (Barnes 1988) or up to 9 mg/kg/day diazinon for 52 weeks (Rudzki et al. 1991).

Renal Effects. A summary of autopsy findings in 76 cases of acute diazinon poisoning described renal signs that included congested kidney and rare renal tract and kidney cortex submucosal petechiae and ecchymoses (Limaye 1966).

A single oral dose of diazinon ranging from 50 to 700 mg/kg produced dose-dependent renal effects in rats. These effects were observed to varying degrees during the first 72 hours following diazinon exposure. Substituting a purified protein diet for Purina lab chow resulted in additional oliguria, in aciduria rather than alkalinuria, and in somewhat more severe hematuria. A low-protein purified diet exacerbated the aciduria. Other renal effects included tubular swelling, capillary loop congestion, glycosuria, proteinuria, and hematuria (Boyd and Carsky 1969). Beagle dogs treated with 5 mg/kg for 8 months showed kidney corticomedullary congestion and capsular adhesions. One dog that died from exposure to 10 mg/kg/day diazinon exhibited localized chronic nephritis, tubular atrophy, and glomeruli with fibrous infiltrations (Earl et al. 1971).

No gross or histological evidence of treatment-related damage to the kidneys after oral exposure to diazinon was observed in New Zealand rabbit dams receiving up to 100 mg/kg/day diazinon during gestation days 6–18 (Harris and Holson 1981), in Sprague-Dawley rats receiving up to 212 mg/kg/day diazinon in feed for 13 weeks (Singh 1988), or up to 12 mg/kg/day for 98 weeks (Kirchner et al. 1991), or in Beagle dogs receiving up to 11.6 mg/kg/day diazinon for 13 weeks (Barnes 1988) or up to 9 mg/kg/day for 52 weeks (Rudzki et al. 1991).

Endocrine Effects. A 16-year-old female who drank an estimated 10 mL of a diazinon formulation (Tik-20) developed pancreatitis after being treated for cholinergic manifestations. A dose could not be calculated because the concentration of diazinon in the liquid was not reported. The pancreatic effects may well have been secondary to the diazinon-induced cholinergic manifestations (Dagli et al. 1981). Acute pancreatitis was also found in two children poisoned with diazinon (Weizman and Sofer 1992).

Pancreatic atrophy and interstitial fibrosis was reported in male Beagle dogs receiving 10 mg/kg/day diazinon in capsule form for 8 months (Earl et al. 1971), but not in females. Atrophy of the pancreatic acini was observed in male Beagle dogs receiving 10.9 mg/kg/day of diazinon from feed for 13 weeks, but not in similarly treated female dogs receiving 11.6 mg/kg/day diazinon (Barnes 1988).

No gross or histological evidence of treatment-related damage to the adrenals after oral exposure to diazinon was observed in Sprague-Dawley rats (15/sex/group) receiving up to 212 mg/kg/day diazinon from feed for 13 weeks (Singh 1988). No gross or histological evidence of treatment-related damage to the adrenals, pituitary, or thyroid glands was observed in Sprague-Dawley rats receiving up to 12 mg/kg/day diazinon for 98 weeks (Kirchner et al. 1991), or in Beagle dogs receiving up to 11.6 mg/kg/day diazinon for 13 weeks (Barnes 1988).

Ocular Effects. Miosis has been reported in humans admitted to the hospital with diazinon poisoning (Shankar 1967).

Exophthalmos has been reported in male Wistar rats receiving single doses of 50–700 mg/kg diazinon by gavage (Boyd et al. 1969; Boyd and Carsky 1969). No ocular effects were reported in Sprague-Dawley rats receiving a single dose of up to 528 mg/kg diazinon and observed for a further 14 days (Chow and Richter 1994); in Sprague-Dawley rats receiving up to 212 mg/kg/day diazinon from feed for 13 weeks (Singh 1988), or up to 12 mg/kg/day for 98 weeks (Kirchner et al. 1991); or in Beagle dogs receiving up

to 11.6 mg/kg/day diazinon from feed for 13 weeks (Barnes 1988) or up to 9 mg/kg/day for 52 weeks (Rudzki et al. 1991).

Body Weight Effects. Dogs administered diazinon by the oral route in an intermediate-duration study exhibited significant weight loss at doses >10 mg/kg/day. Reduced food intake, diarrhea, and emesis were also reported in this study (Earl et al. 1971). The body weight effects are probably a result of the emesis, diarrhea, generalized emaciation, and anorexia reported in the study. Significant ($p<0.05$) reductions in body weight gain were also found in male Wistar rats treated orally with 0.5 mg/kg diazinon twice a week for 28 weeks. Body weight was significantly greater in 28-week controls (602.5 g) than in diazinon-treated rats (542.0 g) despite the absence of significant deviations in average daily food intake (Anthony et al. 1986). Other male Wistar rats receiving 10 mg/kg/day diazinon by oral gavage for 7 weeks exhibited 22% lower terminal mean body weight than vehicle controls (Ogutcu et al. 2006).

Significant reductions in maternal weight (5.5–9.6%) and weight gain were seen in CD-1 rats receiving 100 mg/kg/day diazinon by gavage during gestation days 6–15 (Infurna and Arthur 1985). This effect was most striking during gestation days 6–10 when the 100 mg/kg/day group lost on average 11 grams while the control group gained 14 grams. A 25% decrease in body weight gain was seen in male Sprague-Dawley rats receiving a single gavage dose of 264 mg/kg diazinon and observed for a period of 14 days (Chow and Richter 1994). Male Sprague-Dawley rats receiving 150.8 mg/kg/day diazinon from feed had a 15% decrease in body weight compared to controls after 6 weeks (Singh 1988). Weight gain in females was unaffected. Emaciation was observed in female Beagle dogs receiving 15.99 mg/kg/day diazinon from feed for 4 weeks; less severe, but still significant, weight loss was observed in male Beagle dogs receiving 14.68 mg/kg/day (EPA 2000a). Significantly reduced rates of body weight gain were observed in male Beagle dogs receiving 10.9 mg/kg/day diazinon from feed (34%) and in females receiving 5.6 mg/kg/day (33%) for 13 weeks (Barnes 1988). Reduced body weight gain was also noted in male Beagle dogs receiving 4.7 mg/kg/day diazinon for 52 weeks (Rudzki et al. 1991). A clear dose-response for body weight gain was not detected in similarly-treated female dogs, but the highest dose level (9.1 mg/kg/day) resulted in a 19% reduction in body weight gain (Rudzki et al. 1991).

No effects on body weight were observed in New Zealand rabbit dams receiving 100 mg/kg/day diazinon by gavage during gestation days 6–18 (Harris and Holson 1981). No effect on body weight was observed in female Wistar rats receiving up to 1.35 mg/kg/day from feed for 92 days (Davies and Holub 1980a); in Wistar rats of both sexes receiving 0.21 mg/kg/day from feed for 7 days or 2.86 mg/kg/day for 30 days (Davies and Holub 1980b); and in Sprague-Dawley rats receiving up to 212 mg/kg/day from feed for

13 weeks (Singh 1988), 0.18 mg/kg/day from drinking water for 6 months (Lox and Davis 1983), or up to 12 mg/kg/day for 98 weeks (Kirchner et al. 1991). No effects on body weight were observed in male Beagle dogs receiving 5 mg/kg/day and females receiving 10 mg/kg/day in capsules daily for 8 months (Earl et al. 1971).

Metabolic Effects. Metabolic acidosis was reported in patients who had ingested 240–916 mg/kg diazinon (Klemmer et al. 1978).

No effect on blood electrolytes was observed in Sprague-Dawley rats receiving up to 12 mg/kg/day diazinon orally for 98 weeks (Kirchner et al. 1991).

3.2.2.3 Immunological and Lymphoreticular Effects

A summary of autopsy findings of 76 cases of acute diazinon poisoning described signs that included congested spleen (Limaye 1966).

Single oral administration of 50–700 mg/kg diazinon to male albino Wistar rats resulted in a reduction in spleen weight (35%) and splenic red pulp contraction, reduced thymus weight, and thymic atrophy ranging from minor to near total loss of thymocytes (Boyd and Carsky 1969). In an intermediate-duration study of dogs administrated oral doses of 2.5–20 mg/kg/day diazinon, the spleen of an anorexic and emaciated male dog given 10 mg/kg/day diazinon was markedly shrunken and pale in appearance with moderate atrophy in the splenic pulp prior to death after 232 days of exposure (Earl et al. 1971). The splenic atrophy reported in this study may be a result of the generalized emaciated condition of the dog due to diarrhea, emesis, and anorexia, as reported in the study.

Repeated oral administration of diazinon to mice (50 mg/kg/day for 30 days) resulted in significantly increased levels of interleukin-10 in splenic lymphocyte subpopulations CD4+, CD8+, and B cells and significantly decreased levels of interferon-γ in B cells (Alluwaimi and Hussein 2007). These results indicate a diazinon-induced effect on cytokines involved in the regulation of cellular and humoral responses.

No gross or histological evidence of treatment-related damage to the spleen or thymus was observed in Sprague-Dawley rats receiving up to 212 mg/kg/day diazinon from feed for 13 weeks (Singh 1988), or up

to 12 mg/kg/day for 98 weeks (Kirchner et al. 1991), or in Beagle dogs receiving up to 11.6 mg/kg/day diazinon for 13 weeks (Barnes 1988) or up to 9 mg/kg/day for 52 weeks (Rudzki et al. 1991).

The highest NOAEL values and all reliable LOAEL values for immunological and lymphoreticular effects in each species and duration category are presented in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

In humans, typical signs and symptoms of cholinesterase poisoning have been widely reported following intentional or accidental ingestion of diazinon (Balani et al. 1968; Bichile et al. 1983; Dagli et al. 1981; Hata et al. 1986; Jaksa and Palahniuk 1995; Kabrawala et al. 1965; Klemmer et al. 1978; Poklis et al. 1980; Reichert et al. 1977; Wadia et al. 1974; Wedin et al. 1984). Reported signs and symptoms of diazinon poisoning included vomiting, abdominal pain, giddiness, excessive sweating, diarrhea, brachycardia, tachycardia, muscle fasciculations, hyperreflexia, restlessness, constricted pupils, miosis, clonus, weakness, bronchospasm, stupor, and coma. In a few of these reports, oral diazinon dose estimates ranged from approximately 200 to 1,000 mg/kg (Klemmer et al. 1978; Poklis et al. 1980). In one case, a neurological examination showed lateral nystagmus and gross incoordination (Bichile et al. 1983). In some cases, measurements of plasma and blood ChE activities indicated significant reduction (Klemmer et al. 1978). Diazinon-poisoned patients responded well to ChE-reactivating agents such as atropine and pralidoxime (Dagli et al. 1981; Kamha et al. 2005; Klemmer et al. 1978). Autopsy findings in patients who died following acute diazinon poisoning include spinal hemorrhage and congestion, swelling, and hemorrhage of the brain (Limaye 1966; Poklis et al. 1980).

As discussed in detail in Section 3.5. Mechanisms of Action, diazinon poisoning is characterized by the inhibition of AChE in the central and peripheral nervous system. AChE is also present in erythrocytes (RBCs). In *in vitro* assays, roughly equivalent inhibition of AChE in RBCs and neural tissues is produced by a given concentration of organophosphates such as diazinon (Iyaniwura 1991). Therefore, inhibition of RBC AChE can be used as a surrogate indicator of the extent of inhibition of neural AChE. Blood plasma also contains other cholinesterases. In humans, plasma ChE is almost exclusive composed of butyrylcholinesterase, which is capable of hydrolyzing acetylcholine and butyrylcholine *in vitro*. The *in vivo* substrate of plasma ChE is unknown. In general, plasma ChE can be inhibited by diazinon at lower levels of exposure than those required to inhibit neural or RBC AChE (Barnes 1988; Singh 1988). Plasma ChE activity is considered to be a sensitive indicator of exposure to organophosphates such as diazinon, but not an indicator of a neurologic effect.

Results of a few controlled studies of human subjects were submitted to the U.S. EPA Office of Prevention, Pesticides and Toxic Substances (OPPT) (EPA 2001). Inhibition of plasma ChE was observed following ingestion of gelatin capsules containing diazinon (EPA 2001). Single doses of 0.12 or 0.2 mg diazinon/kg (purity not specified in the data evaluation record available to ATSDR) resulted in approximately 40 and 60 % inhibition of plasma ChE, respectively. Approximately 90% inhibition was observed in a single volunteer given a 0.3 mg/kg dose of diazinon. Maximum inhibition of plasma ChE in these volunteers was achieved between 4 and 8 hours postdosing. Recovery began 24 hours postdosing, but was only about 70% complete in some volunteers at 15 days postdosing. Although plasma ChE inhibition was noted, RBC AChE was not inhibited and there were no clinical signs of treatment-related neurotoxicity even at the highest dose tested.

In a repeated-dose oral investigation, four male volunteers were administered 0.03 mg diazinon/kg/day (purity 99.5%) in gelatin capsules at breakfast for 28–31 days (EPA 2001). Maximum plasma ChE inhibition reached 47–56% near the end of the treatment period. Recovery was 86–92% by day 28 following the cessation of treatment. There was no apparent treatment-related effect on RBC AChE activity.

In another controlled human study, diazinon (purity not specified in the EPA summary review available to ATSDR) was administered to male volunteers (apparently three males per dose level) at doses of 0.02, 0.025, or 0.05 mg/kg/day (EPA 2001). There was no indication of treatment-related effects on plasma ChE activity following dosing at 0.02 mg/kg for up to 37 days. At 0.025 mg/kg/day, a 23% plasma ChE inhibition was noted from day 12 through day 43. The 0.05 mg/kg/day dose level resulted in 40% plasma ChE inhibition after 5 days of treatment. No treatment-related effects on RBC AChE activity were seen at any of the dose levels.

Results of animal studies support the findings in humans of diazinon-induced neurotoxicity. For example, single oral gavage doses in the range of 75–300 mg/kg, administered to rats (Boyd and Carsky 1969; Chow and Richter 1994; EPA 1996, 2000a; Moser 1995; Moser et al. 2005) or rabbits (Harris and Holson 1981), resulted in signs of cholinergic stimulation such as muscle fasciculations, tremors, miosis, lacrimation, diarrhea, gait changes, and hypoactivity. Robens (1969) reported cholinergic signs in pregnant rabbits administered technical diazinon (purity unspecified) by daily oral gavage on gestation days 5–15 at a dose level of 30 mg/kg/day and in hamsters dosed on gestation days 6–8 at a level of 0.125 mg/kg/day. However, no supporting studies were located to confirm clinical signs of diazinon-

induced neurotoxicity at these relatively low acute dose levels. In a 92-day feeding study in rats, daily doses of 168 mg/kg/day (females) or 212 mg/kg/day (males) resulted in signs of cholinergic stimulation, but doses of 15 and 19 mg/kg/day, respectively, did not elicit clinical signs of neurotoxicity (Singh 1988). Cholinergic signs (muscle fasciculations, emesis, and/or diarrhea) were reported in 3/3 male and 3/3 female dogs administered diazinon in the food at a concentration resulting in a calculated dose of 20 mg diazinon/kg/day for 8 months; only 1/6 dogs in the next lower dose group (10 mg/kg/day) exhibited cholinergic signs (Earl et al. 1971). Similarly-treated swine exhibited clinical signs of neurotoxicity at a dose level of 10 mg/kg/day, but not at 5 mg/kg/day (Earl et al. 1971). In a chronic-duration rat study, 98 weeks of diazinon treatment in the food resulted in no treatment-related clinical signs of neurotoxicity at doses up to approximately 12 mg/kg/day (the highest exposure level) (Kirchner et al. 1991). No clinical signs of neurotoxicity were observed in dogs administered diazinon in the diet for up to 52 weeks at concentrations resulting in doses as high as 9 mg/kg/day (Kirchner et al. 1991).

In an extensive study of diazinon-induced neurological effects following single oral dosing, Sprague-Dawley rats of both sexes were treated by gavage with diazinon (88% purity) at doses of 0, 2.5, 150, 300, or 600 mg/kg and observed in a functional observation battery (FOB) of tests (Chow and Richter 1994). Signs of neurotoxicity were seen only at the expected time of peak effect (9–11 hours postdosing) and not at weeks 1 or 2 posttreatment. At the 150 mg/kg dose level, decreased rearing in a 2-minute period and suppressed maze activity (females only), repetitive opening and closing of the mouth, ataxia, and abnormal gait were noted. Additional treatment-related effects at the next higher dose (300 mg/kg) included altered fecal consistency, soiled fur, stained nose, impaired righting reflex and hindlimb extensor reflex, decreased rearing in a 2-minute period and suppressed maze activity (males), tremors, body twitch, and lowered arousal (females only). Treatment at 600 mg/kg resulted in impaired respiration, lacrimation, reduced forelimb and hindlimb grip strength, decreased hindlimb foot splay, abnormal hindlimb positioning, decreased tail pinch response, lowered arousal level (males), and reduced touch response (females). No treatment-related gross or histopathologic lesions were observed in brain, spinal cord, peripheral nerves, skeletal muscle, eyes, or optic nerve at doses up to and including the highest dose tested (600 mg/kg).

Most available oral animal studies include assessments of diazinon-induced changes in RBC and/or neural AChE activity. Many of these studies were particularly designed to assess AChE activity at diazinon doses below those eliciting clinical signs of neurotoxicity. Diazinon-induced decreased AChE activity may be a sensitive indicator of neurotoxicity, and a 20–59% inhibition of neural or RBC AChE is considered a less serious effect in the absence of more serious indicators of neurotoxicity. Results of

several rat and dog studies identified diazinon-induced RBC and/or brain AChE inhibition of 20% or more following acute-, intermediate-, and chronic-duration oral exposure at doses in the range of 2–15 mg/kg/day (Barnes 1988; EPA 1996, 2000a; Makhteshim-Agan 1989; Trutter 1991). For example, single oral gavage dosing of rats at 2.5 mg/kg resulted in 40% RBC AChE inhibition (EPA 2000a). In a 28-day feeding study, male and female rats receiving diazinon at 2.4 mg/kg/day exhibited 38% RBC AChE inhibition by the end of the first week of treatment (EPA 1996). Davies and Holub (1980a) reported 9, 20, and 22% RBC AChE inhibition in female rats receiving diazinon (99.2% purity) in the diet for 42 days at concentrations of 2, 3, and 4 ppm (0.18, 0.27, and 0.36 mg/kg/day), respectively. This study was specifically designed to assess low-dose cholinesterase responses to oral diazinon and serves as the principal study for deriving an intermediate-duration oral MRL for diazinon (see Appendix A). Administration of diazinon in the diet of male and female rats for 98 weeks at a concentration resulting in a dose level of approximately 5 mg/kg/day caused 26–28% RBC AChE inhibition and 24–29% brain AChE inhibition (Kirchner et al. 1991). The next lower dose level (0.07 mg/kg/day in the female rats) represented a NOAEL and serves as the basis for deriving a chronic-duration oral MRL for diazinon (see Appendix A).

Available single and repeated-dose oral studies in animals demonstrate that significant diazinon-induced plasma ChE inhibition occurs at doses lower than those required to produce significant RBC AChE inhibition and that RBC AChE inhibition is a somewhat more sensitive indicator of effect than brain AChE inhibition (Barnes 1988; Davies and Holub 1980a; Kirchner et al. 1991; Rudzki et al. 1991; Singh 1988; Timchalk et al. 2005). Peak cholinesterase inhibition is typically observed between 6 and 12 hours following single oral dosing (Chow and Richter 1994; Timchalk et al. 2005). In a longer-term (90-day) dietary rat study, diazinon-induced plasma ChE and RBC AChE inhibition increased in severity with exposure duration to a peak at approximately 35 days, after which the severity of the inhibition remained relatively constant (Davies and Holub 1980a). Available animal data indicate that females may be more sensitive than males to diazinon-induced cholinesterase inhibition, particularly with respect to brain AChE inhibition (Barnes 1988; Davies and Holub 1980b; EPA 1996, 2000a; Singh 1988; Trutter 1991).

Limited animal data were located regarding potential for diazinon to elicit other neurophysiologic or neurohistopathologic effects. There were no indications of histopathologic lesions in central and peripheral nervous tissue samples from rats administered diazinon once by oral gavage at doses up to 600 mg/kg (Chow and Richter 1994) or in rats administered diazinon in the diet for 90 days at concentrations resulting in doses as high as 212 mg/kg/day (Singh 1988). No clinical signs or

histopathologic evidence of diazinon-induced delayed neuropathy were seen in hens following oral administration of 11.3 mg diazinon/kg on 2 days (21 days apart) (Jenkins 1988).

Refer to Section 3.2.2.6, Developmental Effects, for information regarding diazinon-induced neurodevelopmental effects.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are presented in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to diazinon. Limited information is available regarding the reproductive toxicity of diazinon in orally-exposed laboratory animals. No adverse effects on reproduction were reported for four generations of female Sprague-Dawley rats fed diazinon in the diet at a concentration resulting in a dose of 0.05 mg/kg/day during gestation and lactation for 60 days prior to weaning (Green 1970). No adverse effect on fertility was observed, as all females became pregnant. Apparently, diazinon exposure increased the average number of pups per litter compared to undosed controls (9.7–11.1 as opposed to 6.2–8) for all five generations (F_0–F_4). Oral administration of diazinon to male albino rats at dose levels of 1.5 or 3 mg/kg/day for 65 days resulted in significantly decreased reproductive tissue weights, increased percentage of dead and morphologically abnormal spermatozoa, decreased plasma testosterone levels, and decreased fertility as assessed by conception rates of untreated females mated to diazinon-treated males (Abd El-Aziz et al. 1994). In a study of hybrid mice, litter size was reduced by 20% at oral maternal diazinon doses of 0.18, but not at 9 mg/kg/day relative to controls (Spyker and Avery 1977). A 14% reduction in maternal weight gain was observed at both doses. Male and female Beagle dogs were given daily capsules containing diazinon in corn oil at doses ranging from 2.5 to 20 mg/kg/day for 8 months (Earl et al. 1971). Testicular atrophy with completely arrested spermatogenesis was observed in the one male dog of the 10 mg/kg/day group that lost weight and evidenced other gross pathological changes. All three male dogs in the 20 mg/kg/day group suffered similar effects (testicular atrophy observed in 2/3, arrested spermatogenesis observed in the other dog).

Administration of diazinon at 10, 20, or 100 mg/kg/day by oral gavage during gestation days 6–15 in CD-1 rats had no significant effect on litter sizes or numbers of viable fetuses (Infurna and Arthur 1985). Maternal toxicity was noted at 100 mg/kg/day with a significant reduction in feed consumption and body

weight gain. In New Zealand rabbits dosed by gavage at 7, 25, or 100 mg/kg/day diazinon during gestation days 6–18, no treatment-related effects were seen in number of implantations, proportion of live, dead or resorbed fetuses, fetal weights, or fetal sex ratios (Harris and Holson 1981). The highest dose level (100 mg/kg/day) resulted in the death of 9/22 dams.

No gross or histological evidence of treatment-related damage to reproductive tissues (ovaries, uterus, vagina, epididymides, seminal vesicles, testes) was observed in Sprague-Dawley rats exposed to up to 168 mg/kg/day diazinon (males) or 212 mg/kg/day (females) for 13 weeks via feed (Singh 1988), or up to 10 mg/kg/day (males), or 12 mg/kg/day (females) for 98 weeks (Kirchner et al. 1991), or in Beagle dogs exposed to up to 10.9 mg/kg/day (males) or 11.6 mg/kg/day (females) for 13 weeks (Barnes 1988).

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are presented in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects of diazinon in orally-exposed humans. Mouse studies provide evidence that lactational exposure to diazinon does not cause developmental toxicity. Results of other studies in rats, mice, hamsters, and rabbits also have not demonstrated dose-response effects on the developing mammalian fetus or neonate. The adverse effects reported for pups have been suggested to derive from diazinon impairment of placental transport of nutrients or maternal regulation of fetal growth, or directly via antagonism to cholinergic development of the fetus. No significant effects were seen in rabbit offspring at maternally lethal doses.

In a teratology study, mouse dams were administered doses of 0, 0.18, or 9 mg/kg/day diazinon (technical grade, purity not specified) in peanut butter throughout gestation. The study found no maternal toxicity at any of the doses tested. Significantly elevated ($p<0.05$) mortality (12%, 18 of 150) was observed in the high dose group at weaning (postpartum day 28), but not in the low dose group (2%, 3 of 134), when compared with controls (6%, 19 of 311). Histological examination indicated that the majority of these pups died from pulmonary congestion and mucosal infiltration consistent with acute bronchitis. Diazinon treatment did not adversely affect postweaning mortality. Lactational exposure to diazinon did not have any adverse effect (Barnett et al. 1980). A previous study using the same protocol and dose regimen exposed dams throughout gestation to doses of 0, 0.18, or 9 mg/kg/day diazinon in peanut butter (Spyker and Avery 1977). Dams exposed to either diazinon dose experienced reduced weight gain (86% that of

controls, $p<0.05$) during pregnancy, but gestation length was not significantly affected. Pup weight gain during the first 14 weeks after parturition was significantly ($p<0.05$) less at the 9 mg/kg/day dose than at the 0 and 0.18 mg/kg/day doses. With the exception of contact placing and sexual maturity, which were delayed with respect to controls ($p<0.05$) in the low dose pups, developmental ontogeny as measured by numerous parameters was not significantly affected by diazinon exposure. No teratological effects were evident. However, both diazinon groups displayed endurance and coordination deficits during neuromuscular function tests (rod cling and inclined plane), and 9 mg/kg/day offspring also displayed slower running speed in a Lashley III maze and reduced swimming endurance. Morphologically, the brains of 9 (but not 0.18) mg/kg/day offspring had focal abnormalities in the forebrain area, including dense aggregations of atypical chromatin-containing cells. Among the offspring of hybrid mouse dams exposed to 0.18 or 9 mg/kg/day diazinon during gestation days 1–18, females from the 9 mg/kg/day group showed a 33% decrease of serum IgG_1 levels 101 days after birth (Barnett et al. 1980). These levels were normal at 400 and 800 days after birth, and no effects on serum Ig levels were observed in male offspring at either dose. Fetal exposure to low levels of diazinon may result in functional deficits in otherwise normal animals that can only be detected by systemic behavioral evaluation. These neural dysfunctions and pathologies might occur either indirectly through diazinon impairment of placental transport of nutrients or maternal regulation of fetal growth, or directly via antagonism to cholinergic development of the fetus (Spyker and Avery 1977).

Pregnant Golden Syrian hamsters were orally exposed by gavage to diazinon during organogenesis (0.125 mg/kg/day to eight dams on gestation day 6, 7, and 8; 0.25 mg/kg/day to five dams on gestation day 7 or 8). All dams survived, but displayed cholinergic signs of diarrhea, salivation, and ataxia. No terata were observed at either dose, nor were average number of fetuses per litter, fetal mortality, or average fetal weight adversely affected. Thus, at maternally toxic doses, diazinon was not feto- or developmentally toxic to hamsters (Robens 1969).

Diazinon was not fetotoxic or developmentally toxic to rabbits at maternally lethal doses. When pregnant New Zealand white rabbits were orally exposed by gel capsules to 7 or 30 mg/kg/day diazinon on day 15 of gestation, 6/8 of the dams in the high dose group died. The dams in this dose group also exhibited severe cholinergic signs. However, no terata or dose-related embryotoxic effects (average number of fetuses per litter, fetal mortality, average fetal weight) were observed even at maternally toxic doses (Robens 1969). In a study of New Zealand rabbit does exposed by gavage to 7, 25, or 100 mg/kg/day diazinon during gestation days 6–18 and sacrificed on gestation day 25, no significant treatment-related fetal malformations or skeletal malformations were observed in the offspring (Harris and Holson 1981).

Nine of the 22 dams in the 100 mg/kg/day group died during the study, indicating that significant maternal toxicity occurred at this dose.

An increased incidence of rudimentary ribs at T-14 was observed in CD-1 rats receiving 100 mg/kg/day diazinon during gestation days 6–15 (Infurna and Arthur 1985). This finding was accompanied by severe weight loss in the dams and this developmental effect was considered by the authors of this study to be secondary to maternal toxicity.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are presented in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

Several epidemiological studies have reported increased incidence of cancers in humans who were concurrently or sequentially exposed to a number of insecticides, including diazinon. Some degree of oral exposure is presumed to have occurred. However, it is not possible to attribute the increased cancer incidence exclusively to diazinon exposure.

A case-control study suggested a possible link between family gardening use of diazinon (and other insecticides) and increased incidence of childhood brain cancer (type unspecified). However, this report gave no indication of level, duration, or frequency of exposure to diazinon (or to other insecticides) (Davis et al. 1993). Another case-control study suggested a positive association between an increased incidence of non-Hodgkin's lymphoma in farmers compared to nonfarmers. The report attributed the increased incidence of lymphomas to handling of organophosphorus insecticides, including diazinon (Cantor et al. 1992). A third case-control study suggested an association between an increased incidence of multiple myelomas and high exposure to insecticides, including diazinon. Actual exposure to diazinon was reported in 2/698 (0.3%) of the cases and 5/1,683 (0.3%) of the controls (Morris et al. 1986).

A cancer bioassay was conducted with groups of Fischer 344 rats (50/sex/group) exposed *ad libitum* to estimated dietary doses of 20 or 40 mg/kg/day diazinon for 103 weeks; groups of 25 rats/sex served as unexposed controls. Tissue masses were noted especially in high-dose males and low-dose females, and tachypnea incidence was elevated in exposed groups. A variety of neoplastic and nonneoplastic lesions was observed with approximately equal frequency in the control and dosed groups in both sexes. An increase in the common lesion of endometrial stromal polyps observed in female rats (control=2/23, low

dose=8/43, high dose=11/49) was considered unrelated to diazinon exposure. In male rats, lymphomas and leukemias were significantly ($p<0.011$) elevated in the low dose group (25/50), but not in the high dose group (12/50), relative to controls (5/25). The study concluded that diazinon was not carcinogenic under the conditions of this assay for either sex of Fischer 344 rats (NCI 1979). In another cancer bioassay, groups of $B6C3F_1$ mice (50/sex/group) were exposed for 103 weeks to estimated dietary doses of 13 or 26 mg/kg/day diazinon; groups of 25 mice/sex served as unexposed controls. A number of neoplastic and nonneoplastic lesions, essentially considered nontreatment-related, were observed in both the control and treated mice. An elevation in hepatocellular adenomas and carcinomas was observed in low-dose (20/46), but not high-dose (13/48) male mice, relative to controls (5/21). The study concluded that diazinon was not carcinogenic under the conditions of this assay for either sex of $B6C3F_1$ mice (NCI 1979).

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to diazinon.

In laboratory animal studies, the acute dermal toxicity of diazinon and its formulations varies profoundly, largely as the result of sample aging and differences in purity of formulation, particular solvent, and area of exposed skin. In general, aged diazinon samples that contained more impurities were more toxic (Gaines 1960). The use of an occlusive dressing after dermal application usually increases dermal toxicity because it enhances sweating and dermal absorption. Dermal LD_{50} values were determined in Sherman rats of both sexes (Gaines 1960). Diazinon was applied to a shaved dermal area of approximately 13.5 cm^2. LD_{50} values were 900 and 455 mg/kg for males and females, respectively. Among New Zealand rabbits dermally exposed for 24 hours to 2,020 mg/kg diazinon, 2/5 females and 0/5 males died within 2 days after exposure ceased (EPA 1990).

The LD_{50} values and doses associated with death in each species and duration category are shown in Table 3-3.

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

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
ACUTE EXPOSURE							
Death							
Rat (Sherman)	once				900 M mg/kg (LD50)	Gaines 1960	Technical grade diazinon (purity not specified).
					455 F mg/kg (LD50)		
Systemic							
Human	72 hr	Dermal	1 Percent (%)			Lisi et al. 1987	
Gn Pig (Hartley)	24 hr	Dermal	5 F Percent (%)	10 F Percent (%) (erythema)		Matsushita et al. 1985	Diazinon (purity not specified).
Rabbit (New Zealand)	4 hr	Dermal		0.5 B colonies per 100 milliters (erythema, slight edema)		EPA 1990	
Immuno/ Lymphoret							
Human	once		1 Percent (%)			Lisi et al. 1987	
Neurological							
Rat (Sprague-Dawley)	once (C)			65 F mg/kg (52% RBC AChE inhibition)		Abu-Qare and Abou-Donia 2001	

Table 3-3 Levels of Significant Exposure to Diazinon - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
INTERMEDIATE EXPOSURE								
Systemic								
Rat (dark agouti)	12 wk 7 d/wk 1 x/d	Hepatic		114 F mg/kg	(elevated fecal porphyrin)		Bleakley et al. 1979	
Immuno/ Lymphoret								
Gn Pig (Hartley)	24 hr			0.05 F Percent (%)	(moderate delayed contact sensitivity)		Matsushita et al. 1985	

AChE = acetylcholinesterase; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gn pig = guinea pig; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; RBC = red blood cell; x = time(s); wk = week(s)

3.2.3.2 Systemic Effects

No studies were located regarding musculoskeletal, renal, ocular, or body weight effects in humans after dermal exposure to diazinon. No studies were located regarding cardiovascular, hematological, musculoskeletal, renal, endocrine, or ocular effects in animals after dermal exposure to diazinon.

Respiratory Effects. A 56-year-old female gardener, dermally exposed to spilled diazinon of unknown purity, developed respiratory distress as one of the cholinergic symptoms of AChE inhibition. The victim exhibited pulmonary edema with bilateral lung crepitations and tachypnea (Lee 1989).

Nasal discharge was observed in New Zealand rabbits of both sexes following dermal exposure for 24 hours to 2,020 mg/kg diazinon (EPA 1990).

Cardiovascular Effects. A 56-year-old female gardener, dermally exposed to spilled diazinon of unknown purity, developed sinus tachycardia with no evidence of infarction and showed increased cardiac enzyme (serum glutamate oxalate transaminase, total lactate dehydrogenase creatine phosphokinase) levels. The victim was diagnosed on discharge with acute left ventricular failure (Lee 1989).

Gastrointestinal Effects. Two female gardeners, dermally exposed to spilled diazinon of unknown purity, developed signs of acute pancreatitis which included abdominal colic, diarrhea, nausea, vomiting, and epigastric pain, as well as elevated serum amylase and urinary diastase levels (Lee 1989).

Both decreased defecation and diarrhea were observed in New Zealand rabbits of both sexes following dermal exposure for 24 hours to 2,020 mg/kg diazinon (EPA 1990).

Hematological Effects. Two female gardeners, dermally exposed to spilled diazinon of unknown purity, developed hypokalemia and leucocytosis (Lee 1989).

Hepatic Effects. Female dark Agouti rats received daily cutaneous doses of either 114 or 229 mg/kg/day diazinon. Significant elevations in total fecal porphyrin excretion were observed at the 114 mg/kg/day dose after 8–12 weeks (3–5-fold), and at the 229 mg/kg/day dose at least by week 12 (4-fold). No concomitant rises in urinary porphyrin excretion were observed. Electrophoretic analysis revealed the presence of isocoporphyrin in the feces. Except for the unexplained lack of urinary

porphyrin, these findings were noted to be biochemically characteristic of human porphyria cutanea tarda, and indicative of disturbed hepatic porphyrin metabolism. However, oral administration of 46 mg/kg/day to another group of rats was without this effect (Bleakley et al. 1979).

Endocrine Effects. Two female gardeners, 56 and 48 years old, dermally exposed to spilled diazinon of unknown purity, developed signs of acute pancreatitis, which included abdominal colic, diarrhea, nausea, vomiting, and epigastric pain, as well as elevated serum amylase and urinary diastase levels. One of the victims was diagnosed on discharge with organophosphate poisoning and diabetes mellitus. The authors of this study noted that acute pancreatitis is frequently a component of organophosphate intoxication, although it is often not recognized as such in the medical literature or by treating physicians (Lee 1989).

Dermal Effects. Dermal exposure to diazinon resulted in contact dermatitis in farm workers (Matsushita et al. 1985). But, according to another report, a 1% diazinon solution in a skin patch did not elicit an irritation or cause sensitization in humans (Lisi et al. 1987).

Skin erythema was noted in guinea pigs dermally exposed to 10 and 20% diazinon, but not at lower concentrations of 0.5–5.0% (Matsushita et al. 1985). Well defined erythema and slight edema were observed in New Zealand rabbits of both sexes following dermal exposure for 4 hours to 0.5 mL of diazinon (EPA 1990).

Body Weight Effects. Body weight was unaffected in New Zealand rabbits dermally exposed to up to 2,020 mg/kg diazinon for 24 hours and observed for 14 days (EPA 1990).

3.2.3.3 Immunological and Lymphoreticular Effects

One percent diazinon in "pet" (presumably petroleum ether) has been tested for allergic reactions by patch tests in 294 volunteers examined after 48 and 72 hours of dermal contact (Lisi et al. 1987). The 1% diazinon solution on a skin patch did not elicit allergic reactions in any of the volunteers studied.

Diazinon has also been tested for delayed contact hypersensitivity following skin application to guinea pigs. Induction concentrations of diazinon were reported as 5% (intradermal) and 25% (topical). At both 24 and 48 hours after challenge in the guinea pig maximization test, response to a 0.05% diazinon challenge was scored as grade III (moderate, 30% sensitization rate), and to 0.5% diazinon as grade V

(extreme, 100% rate). When cross-sensitization was tested using a challenge of 0.2 or 2% benomyl, allergenicities were grade I (0%) and grade III (30%), respectively (Matsushita et al. 1985). Skin sensitization did not occur in Hartley guinea pigs treated 11 times over a 36-day period with 0.5 mL of diazinon (Kuhn 1989b).

3.2.3.4 Neurological Effects

Two female gardeners, 56 and 48 years old, dermally exposed to spilled diazinon of unknown purity, developed cholinergic organophosphate poisoning symptoms. The victims exhibited signs and symptoms which included cyanosis, frothing at the mouth, drowsiness, nausea, vomiting, abdominal colic, diarrhea, tachypnea, miosis, and sinus tachycardia with no evidence of infarction. One victim showed significantly depressed plasma ChE levels (Lee 1989).

Tremors were reported in female (but not male) New Zealand rabbits after 24 hours of dermal exposure to 2,020 mg/kg diazinon (EPA 1990).

No studies were located regarding OPIDN in humans or in animals after dermal exposure to diazinon.

3.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following dermal exposure to diazinon.

3.2.3.6 Developmental Effects

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

3.2.3.7 Cancer

Several epidemiological studies have reported increased incidence of cancers in humans who were concurrently or sequentially exposed to a number of insecticides, including diazinon. Some degree of dermal exposure is presumed to have occurred. However, it is not possible to attribute the increased cancer incidence exclusively to diazinon exposure.

A case-control study suggested a possible link between family gardening use of diazinon (and other insecticides) and increased incidence of childhood brain cancer (type unspecified). However, this report gave no indication of level, duration, or frequency of exposure to diazinon, or to other insecticides (Davis et al. 1993). Another case-control study suggested a positive association between an increased incidence of non-Hodgkin's lymphoma in farmers compared to nonfarmers. The report attributed the increased incidence of lymphomas to handling of organophosphorus insecticides, including diazinon (Cantor et al. 1992). A third case-control study suggested an association between an increased incidence of multiple myelomas and high exposure to insecticides, including diazinon. Actual exposure to diazinon was reported in 2/698 (0.3%) of the cases and 5/1,683 (0.3%) of the controls (Morris et al. 1986).

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

3.2.4 Other Routes of Exposure

This section contains diazinon toxicity data from injection studies that reported effects not observed in studies using natural (inhalation, oral, or dermal) exposure routes. *In vitro* diazinon toxicity data are included as well.

Slotkin and coworkers (Jameson et al. 2007; Slotkin et al. 2006a, 2006b, 2007) reported evidence of diazinon-induced neurodevelopmental effects in the forebrain and brainstem of neonatal rats at dose levels near or below those eliciting significant cholinesterase inhibition, the most commonly-observed indicator of diazinon toxicity. In these studies, newborn rats were subcutaneously injected with diazinon on postnatal days 1–4 at doses ranging from 0.5 to 2 mg/kg/day. Slotkin et al. (2006a) noted impaired neuritic outgrowth, evidenced by treatment-related decreased ratio of membrane protein to total protein, and a dose-dependent deficit in choline acetyltransferase activity (a constitutive marker of cholinergic projections) in the absence of an effect on hemicholinium-3 binding to the presynaptic choline transporter (an index of cholinergic neuronal activity). Diazinon-induced up-regulation of 5HT receptors and 5HT transporter was reported by Slotkin et al. (2006b). Diazinon-induced regional suppression of selected fibroblast growth factors, neurotrophic factors that play critical roles in neuronal development and recovery from injury, were reported by Slotkin et al. (2007).

Diazinon inhibited the outgrowth of axon-like processes in mouse N2a neuroblastoma cells *in vitro* at a concentration (1 μM) causing slight AChE inhibition but not affecting cell viability (Flaskos et al. 2007).

3.3 GENOTOXICITY

Chronic occupational exposure to multiple insecticides, including diazinon, has been associated with an increased incidence of chromosomal aberrations and increased sister chromatid exchanges in peripheral blood lymphocytes as compared with nonexposed populations (De Ferrari et al. 1991; Kiraly et al. 1979; See et al. 1990). Some of these exposures are presumed to be by inhalation. However, it is not possible to attribute the results of these studies to diazinon alone, as workers were exposed to up to 80 different insecticides in unknown amounts for variable durations.

Limited information is available regarding the *in vivo* genotoxicity of diazinon. Significantly increased sister chromatid exchanges were noted in peripheral blood lymphocytes from a group of volunteers following exposure to diazinon in a sheep-dip formulation (approximately 45% diazinon); the magnitude of the increase in sister chromatid exchanges was approximately 2-fold greater than the pre-exposure sister chromatic exchange rate (Hatjian et al. 2000). However, the specific role of diazinon in the observed effect could not be determined because the sheep-dip formulation contained other ingredients as well. Diazinon (95% purity) induced mutations in a wing somatic mutation and recombination test (SMART) of *Drosophila melanogaster* (Çakir and Sarikaya 2005). Diazinon did not induce sister chromatid exchanges in the bone marrow of mice administered diazinon (88% purity) in single 100 mg/kg gavage dose (EPA 1990).

Results of *in vitro* laboratory testing for diazinon-induced genotoxicity in mammalian cells and microorganisms are equivocal (see Table 3-4). Diazinon induced gene mutations in one Ames assay of *Salmonella typhimurium* in the presence (but not the absence) of metabolic activation (Wong et al. 1989). The chemical was not mutagenic in other Ames assays either with (Kubo et al. 2002) or without (Kubo et al. 2002; Marshall et al. 1976) metabolic activation. Diazinon did not induce gene mutation in the rec-assay utilizing strains of *Bacillus subtilis* tested without metabolic activation (Shirasu et al. 1976). In one mouse lymphoma mutagenicity assay, diazinon elicited a mutagenic response in the absence of metabolic activation (McGregor et al. 1988). However, mutagenicity was not indicated in a similar assay of mouse lymphoma cells either with or without metabolic activation (EPA 1988). Diazinon induced chromosomal aberrations in Chinese hamster cells with metabolic activation (Matsuoka et al. 1979), but tested negative for chromosomal aberrations in human peripheral blood lymphocytes (Lopez et al. 1986). Negative results were obtained in a test for sister chromatid exchanges in Chinese hamster V79 cells, both with and without metabolic activation (Chen et al. 1982) and in a test for micronuclei in cultured rat hepatocytes (Frölichstahl and Piatti 1996). A weakly positive result was obtained for micronuclei in

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

Species (test system)	End point	Results		References
		With activation	Without activation	
Prokaryotic organisms:				
Bacillus subtilis (rec assay)	Gene mutation	Not done	–	Shirasu et al. 1976
Salmonella typhimurium	Gene mutation	+	–	Wong et al. 1989
S. typhimurium	Gene mutation	Not done	–	Marshall et al.1976
S. typhimurium	Gene mutation	–	–	Kubo et al. 2002
Eukaryotic organisms:				
Mammalian cells:				
Mouse lymphoma cells	Gene mutation	Not done	+	McGregor et al. 1988
Mouse lymphoma cells	Gene mutation	–	–	EPA 1988
Human peripheral blood lymphocytes	Chromosomal aberration	Not done	–	Lopez et al. 1986
Chinese hamster cells	Chromosomal aberrations	+	–	Matsuoka et al. 1979
Chinese hamster cells	Sister chromatid exchange	–	–	Chen et al. 1982
Human peripheral blood lymphocytes	Micronuclei	Not done	(+)	Bianchi-Santamaria et al. 1997
Rat hepatocytes	Micronuclei	–	Not done	Frölichstahl and Piatti 1996
Human primary nasal mucosal cells	DNA damage	Not done	+	Tisch et al. 2002
Transformed PC12 pheochromocytoma cells	Inhibition of DNA synthesis	Not done	+	Qiao et al. 2001
Transformed C6 glioma cells	Inhibition of DNA synthesis	Not done	+	Qiao et al. 2001
Human 1321N1 astrocytoma cells	Inhibition of DNA synthesis	Not done	+	Guizzetti et al. 2005
Fetal rat astrocytes	Inhibition of DNA synthesis	Not done	+	Guizzetti et al. 2005

– = negative result; + = positive result; (+) = weakly positive; DNA = deoxyribonucleic acid

cultured human peripheral blood lymphocytes exposed to diazinon at concentrations ranging from 0.04 to 4 µg/mL (Bianchi-Santamaria et al. 1997). Diazinon-induced deoxyribonucleic acid (DNA) damage was reported in a Comet assay using human primary nasal mucosal cells (Tisch et al. 2002). Diazinon inhibited DNA synthesis in transformed PC12 pheochromocytoma and C6 glioma cells (Qiao et al. 2001), as well as fetal rat astrocytes and human 1321N1 astrocytoma cells (Guizzetti et al. 2005).

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were located regarding absorption after inhalation exposure of diazinon in humans or animals. However, efficient absorption of inhaled diazinon is expected.

3.4.1.2 Oral Exposure

Diazinon is readily absorbed by the oral exposure route. Rapid and extensive absorption was noted following the ingestion of a 0.011 mg/kg dose of diazinon (94% purity) by a group of five volunteers, as evidenced by the excretion of approximately 60% of the administered dose as dialkyl phosphate metabolites in the urine, most (90%) of which was recovered within 14 hours postadministration (Garfitt et al. 2002). Diazinon was detected in several tissues from a woman who had ingested a lethal amount of an estimated 293 mg/kg diazinon formulation ("FERTI-LOME" bagworm spray) containing 10% diazinon suggesting rapid absorption from the gastrointestinal tract (Poklis et al. 1980).

Animal studies also demonstrate rapid absorption of diazinon following oral administration. Wistar WU rats of both sexes were given either a single oral dose of 4 mg/kg or daily doses of 8.0 mg/kg [^{14}C]diazinon for 10 consecutive days. The rapid absorption of diazinon was indicated by the early excretion of radioactivity (Mücke et al. 1970). Similar results were obtained following a single oral dose of 4.0 mg/kg [^{14}C]diazinon to female Beagle dogs where absorption was determined to be at least 85% (Iverson et al. 1975). Within 30 minutes following the oral administration of an 80 mg/kg dose of diazinon (99.8% purity) to eight male Wistar rats, the mean plasma concentration of diazinon exceeded 0.6 mg/L; by 2 hours postadministration, a peak plasma concentration of 1.22 mg/L was achieved (Wu et al. 1996a). In goats given daily oral doses of 0.5 or 5.0 mg/kg/day diazinon for 7 days or a single 150 or 700 mg/kg dose, diazinon was detected in blood from the first day of treatment (Mount 1984). Other

studies demonstrated rapid absorption of orally administered diazinon in sheep (Janes et al. 1973; Machin et al. 1971, 1974) and cows (Abdelsalam and Ford 1986).

3.4.1.3 Dermal Exposure

Absorption of diazinon following dermal exposure has been demonstrated in humans. Volunteers were exposed for 24 hours to [^{14}C]diazinon applied to either the forearm or abdomen in acetone or lanolin wool grease (Wester et al. 1993). Based on the excretion of ^{14}C in the urine, absorption was determined to be 3–4% of the applied dose with no difference related to vehicle or the area applied. In another study, 8-hour occluded dermal application of 100 mg of diazinon (94% purity) on an 80 cm^2 area of the forearm of four volunteers resulted in approximately 0.5% absorption based on the recovery of urinary dialkyl phosphate metabolites (Garfitt et al. 2002). Greater than 90% of the administered dose was recovered from the application site.

No studies were located regarding absorption of diazinon after dermal exposure in animals.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

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

3.4.2.2 Oral Exposure

Samples of stomach contents, blood, bile, adipose tissue, liver, brain, and kidney were collected at autopsy of a woman who ingested a lethal dose estimated at 293 mg/kg of a diazinon formulation ("FERTI-LOME" bagworm spray) containing 10% diazinon (Poklis et al. 1980). The highest concentrations of diazinon were found in the blood, followed by stomach contents and the bile. Lowest concentrations were found in the kidney, followed by adipose tissue and bile. Animal studies support the human data and demonstrate that diazinon is widely distributed in all analyzed tissues in rats (Mücke et al. 1970), sheep (Janes et al. 1973; Machin et al. 1971, 1974), and cows (Abdelsalam and Ford 1986). Although widely distributed via the circulation, it is generally understood that absorbed diazinon is rapidly metabolized and does not accumulate significantly in body tissues. However, Garcia-Repetto et al. (1996) reported detectable levels of diazinon in blood, adipose tissue, muscle, liver, and brain of rats following oral dosing at approximately 23 mg/kg. In blood, adipose tissue, and brain, the levels

decreased with time from 4 to 20 days postdosing. Levels in muscle and liver increased up to 12 and 8 days postdosing, respectively, and decreased thereafter. By 30 days postdosing, detectable levels were no longer observed in blood, adipose tissue, muscle, liver, or brain.

3.4.2.3 Dermal Exposure

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

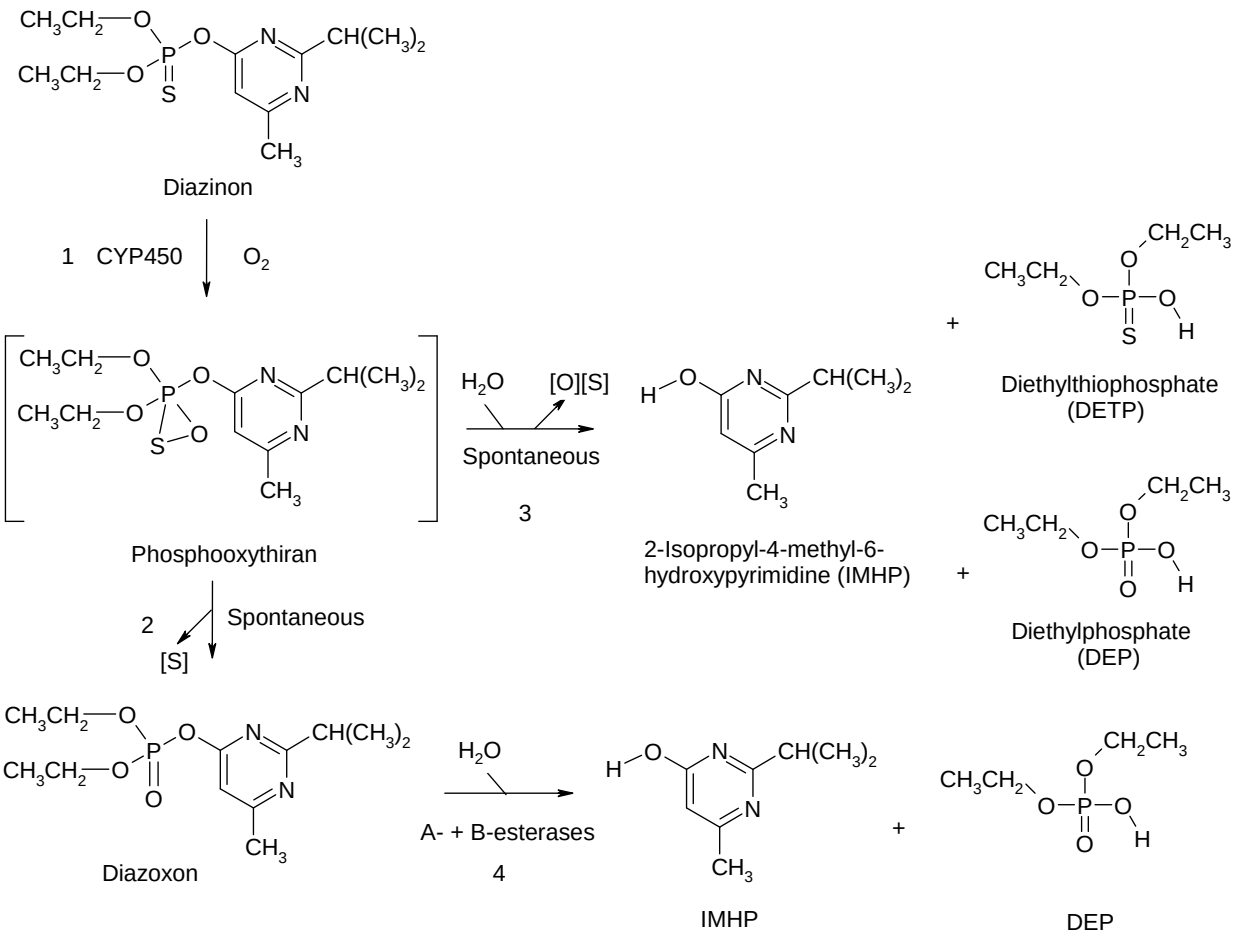
3.4.3 Metabolism

Although diazinon (as parent compound) can elicit mild cholinergic stimulation, its oxygenated metabolite (diazoxon) is mainly responsible for these neurotoxic signs (Wilson 2001). A proposed metabolic scheme for diazinon is presented in Figure 3-3. The CYP450-catalyzed oxidation of diazinon (reaction 1 in Figure 3-3) results in an intermediate (phosphooxythiran), which in turn undergoes spontaneous desulfuration (reaction 2) to form diazoxon. Alternatively, phosphooxythiran may be deactivated via hydrolysis, desulfuration, and deoxygenation (reaction 3) to form metabolites 2-isopropyl-4-methyl-6-hydroxypyrimidine (IMHP), diethylthiophosphate (DETP), and DEP, all of which are excreted in the urine. Detoxification of diazoxon (reaction 4) to IMHP and DEP occurs via hydrolysis catalyzed by hepatic and extrahepatic A-esterases (paraoxonase or PON1) and B-esterases (carboxylesterases) (Fabrizi et al. 1999; Poet et al. 2003; Yang et al. 1971). Results of several *in vitro* assays using human liver cells implicate CYP2C19 as a major P-450 isozyme involved in the formation of diazoxon from diazinon; other P-450 isozymes (e.g., CYP1A2, CYP2B6, CYP3A4, CYP3A5, CYP2D6) are also implicated (Buratti et al. 2003; Kappers et al. 2001; Mutch and Williams 2006; Sams et al. 2004). In rat liver, CYP2C11, CYPA2, and CYP2B1/2 appear to be the major catalyzing agents in the formation of diazoxon from the parent compound, diazinon.

Available data indicate that absorbed diazinon is rapidly metabolized. Wu et al. (1996a) administered diazinon to male Wistar rats at a dose of 80 mg/kg and followed the timecourse of measurable plasma concentrations. Based on the rate of disappearance of diazinon from the plasma, an elimination half-time of 2.86 hours was estimated. These results provide suggestive evidence for the rapid metabolism of absorbed diazinon.

Age-related differences in the detoxification of diazinon and its active metabolite, diazoxon, are apparent, as demonstrated in an *in vitro* assay of rat liver and plasma (Padilla et al. 2004). The results indicated a much lower degree of detoxification by liver and plasma from young rats compared to adult tissues.

Figure 3-3. Putative Pathways of Diazinon Biotransformation



IMHP, DEP, and DETP are urinary metabolites of diazinon

Sources: Kappers et al. 2001; Poet et al. 2004

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No studies were located regarding excretion of diazinon after inhalation exposure in humans or animals.

3.4.4.2 Oral Exposure

Following oral dosing of diazinon (0.011 mg/kg) to four volunteers, rapid absorption, metabolism, and elimination was indicated as evidenced by the excretion of approximately 60% of the administered dose as dialkyl phosphate metabolites (DEP and DETP) in the urine, most (90%) of which was recovered within 14 hours postadministration (Garfitt et al. 2002). Unmetabolized diazinon was not detected. Following a single oral dose of 4.0 mg/kg 2-pyrimidinyl ring-labeled and 4-pyrimidinyl ring-labeled [^{14}C]diazinon to rats, approximately 50% of the dose was excreted within 12 hours of dosing (Mücke et al. 1970). Sixty-nine to 80% of the radioactivity was recovered in the urine and 18–25% was excreted in the feces. Only 5.6% of an ethyl-[^{14}C]diazinon dose was recovered as $^{14}CO_2$ in expired air. No $^{14}CO_2$ was expired from rats given an oral dose of 2-[^{14}C] or 4-[^{14}C]pyrimidine diazinon, indicating that complete degradation of the pyrimidine ring did not take place. Traces of unchanged diazinon were recovered in the feces. Three of the unidentified metabolites recovered in the urine and feces of treated rats accounted for 70% of the total administered dose. The half-life of the ^{14}C-ring labeled diazinon was 12 hours while that of [ethyl-^{14}C]diazinon was 7 hours (Mücke et al. 1970). Recovery of radioactivity in the urine of female Beagle dogs 24 hours after receiving a single oral dose of [^{14}C]diazinon was 85% (53% water-soluble fraction, and two metabolites that no longer had a phosphorothioate group, comprising 10 and 23%). No diazinon was detected in the feces (Iverson et al. 1975). Following oral administration of diazinon to lactating goats, DETP was detected in the urine but not in the milk (Mount 1984).

3.4.4.3 Dermal Exposure

Diazinon urinary metabolites (DEP and DETP) were recovered from volunteers treated by occluded dermal application of 100 mg of diazinon (94% purity) on an 80 cm^2 area of the forearm for 8 hours (Garfitt et al. 2002). Most (90%) of the administered dose was recovered from the application site. Approximately 0.5% was recovered as urinary metabolites. In another human study, volunteers were exposed for 24 hours to 2-pyrimidinyl ring-labeled [^{14}C]diazinon applied to either the forearm or abdomen in either an acetone solution or a lanolin wool grease at doses of approximately 15–20 µg for each application method to test the percutaneous absorption of diazinon (Wester et al. 1993). Daily

complete void urine samples were collected and analyzed for levels of radioactivity for 7 days after dosing. The percentage of the administered dose excreted in the urine was approximately 3–4%.

3.4.4.4 Other Routes of Exposure

Following an intravenous injection of [ethyl-^{14}C]diazinon to female Beagle dogs, approximately 58% of the radioactivity was recovered in the urine within 24 hours as DETP (42%) and DEP (16%). No unchanged diazinon was excreted (Iverson et al. 1975).

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

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

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

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The

numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

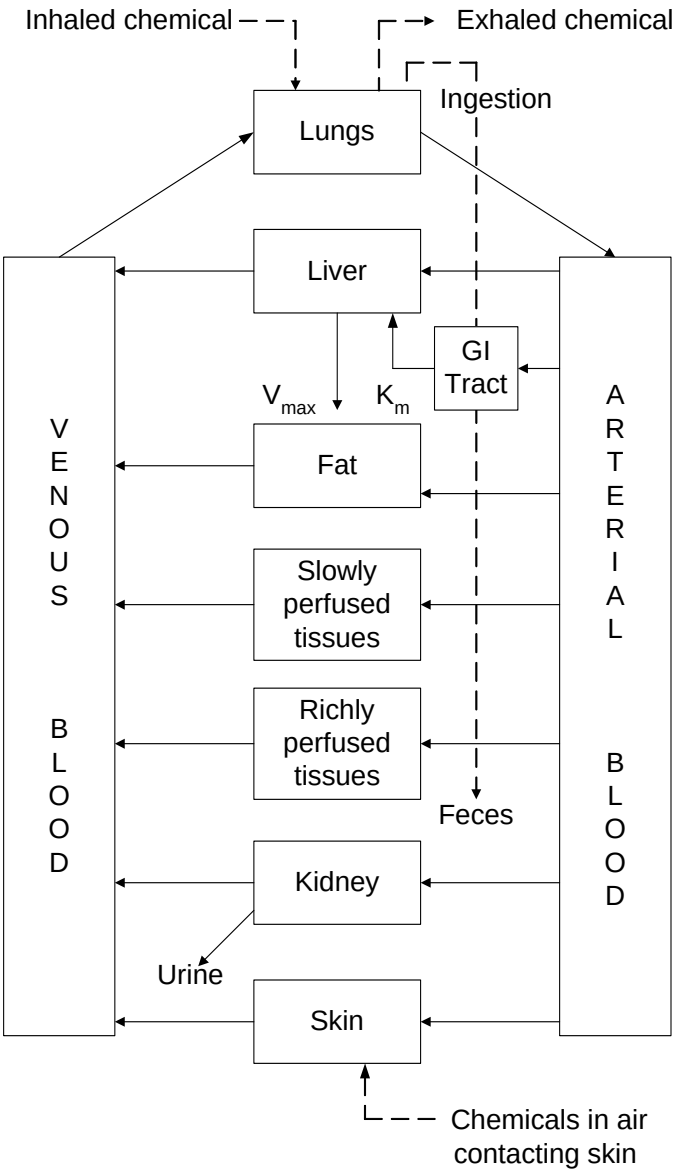
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

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

A physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model has been developed for predicting the absorption, distribution, metabolism, and elimination of diazinon and its metabolites, diazoxon and IMHP, in rats and humans (Poet et al. 2004). The model also quantifies the inhibition of B-esterases (AChE, butylcholinesterase [BuChE], ChE, and carboxylesterase) activities in blood, RBCs, liver, diaphragm, and brain.

Description of the Model. The PBPK/PD model for diazinon (Poet et al. 2004) is based on the PBPK/PD model for chlorpyrifos in rats and humans (Timchalk et al. 2002). Represented tissues include the blood, liver, brain, diaphragm, fat, skin, and other rapidly and slowly perfused tissues connected via arterial and venous blood flows. Portals of entry include oral absorption from a two-compartment model of the gut (for gavage dosing) or zero-order absorption directly into the liver (for dietary exposure), first-order dermal absorption into the skin compartment, and intravenous, and intraperitoneal injection.

Figure 3-4. 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.

Competing metabolism of diazinon to diazoxon or IMHP occurs exclusively in the liver via a CYP450 Michaelis-Menten process. Elimination of parent diazinon is strictly by hepatic metabolism. Detoxification metabolism of diazoxon by the A-esterase, PON, occurs in the blood and liver compartments. A fraction of diazoxon is also eliminated as IMHP as part of the B-esterase inhibition pathway. IMHP is eliminated to urine via first-order transfer to a single compartment. Parameter estimates for physiological volumes and flow rates were taken from the literature (Brown et al. 1997). Metabolic constants were determined using *in vitro* rat data previously published (Poet et al. 2003). Physiological flow rates and metabolic constants were scaled to the 0.74 power of body weight. Diffusion of diazinon and diazoxon across tissues was based on the algorithm of Poulin and Krishnan (1996). Oral absorption and IMHP elimination parameter values were derived from fitting the model to rat and human blood and urine data.

In the liver, brain, diaphragm, and blood, free esterase (resulting from net new esterase synthesized minus esterase degraded) may bind to free diazoxon to form an oxon-esterase complex that may be aged or reversed to yield free esterase and IMHP. The parameters governing these processes were taken from the PBPK/PD model for chlorpyrifos (Timchalk et al. 2002), with subsequent optimization to esterase inhibition data in rats (Poet et al. 2004).

Risk Assessment. The model has not been used in risk assessment. It represents both pharmacokinetic disposition of diazinon and metabolites and pharmacodynamic effect (esterase activity inhibition) for diazoxon in target tissues of rats and humans for multiple routes of exposure.

Validation of the Model. The model was calibrated against rat plasma levels of diazinon, plasma and urine levels of IMHP, ChE activity in blood and diaphragm, AChE activity in brain and RBCs, and BuChE levels in blood and diaphragm of rats given oral bolus doses of 15, 50, or 100 mg diazinon/kg in corn oil vehicle (Poet et al. 2004). The model was validated against observations of plasma, brain, and liver levels and inhibition of plasma ChE and RBC AChE in rats (Tomokuni et al. 1985; Wu et al. 1996a). The sole available human data set was for urinary metabolite levels in humans following single gavage or dermal exposures (Garfitt et al. 2002). For both oral and dermal routes of exposure, parameter values governing urinary excretion rate and dermal absorption, respectively, were modified to achieve visual fit of the model output to the data. The effect of these changes to blood and other target tissue levels was not reported.

Species Extrapolation. The model has been applied to rats and humans. The model structure for both species is identical, with species-specific parameter values used for physiological volumes and flow rates and model-optimized values used for oral absorption. Extrapolation to other species would require data for physiological parameters and oral absorption rates.

High-Low Dose Extrapolation. The model has been evaluated for simulating oral, intravenous, and intraperitoneal doses in rats ranging from 15 to 100 mg/kg. For humans, it has been evaluated for a single oral dose level of 11 μg/kg and a dermal dose of 4 mg/kg.

Interroute Extrapolation. The model is structured to simulate exposures from oral gavage and diet, dermal absorption, and intravenous and intraperitoneal injection.

Strengths and Limitations. The model has been shown to make predictions that are quite similar to observations of blood and tissue levels of diazinon and metabolites from multiple routes of exposure in rats from multiple studies (Poet et al. 2004). The human model also makes predictions of blood, red blood cell, and tissue esterase inhibition, which are important toxicodynamic end points. In humans, the model predicts urine levels of diazinon metabolites from oral and dermal exposures that are very similar to observations; however, the ability of the model to accurately simulate levels of diazinon and diazoxon in human target tissues is unknown. Limitations include the lack of validation of model performance for human blood and tissue levels due to the absence of human data for these end points. An associated limitation is uncertainty in the model to accurately describe esterase inhibition in blood, RBCs, or tissues, including the peripheral and central nervous systems.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

No studies were located in which mechanisms of absorption were assessed for diazinon. It is expected that absorption is accomplished via passive diffusion. Limited information was located regarding mechanisms of distribution of absorbed diazinon. Results of *in vitro* assays indicate that plasma diazinon is predominantly (90%) bound to plasma proteins (Wu et al. 1996a). It is generally understood that diazinon does not appreciably accumulate in any specific body tissues and that absorbed diazinon is rapidly metabolized and eliminated. As discussed in Section 3.4.3, detoxification of diazoxon, the diazinon metabolite responsible for the cholinergic response, is catalyzed by A- and B-esterases. The efficacy of diazinon as an effective insecticide is attributed to deficiencies in these esterases, particularly

among target insects. No information was located regarding mechanisms of elimination and excretion of parent compound or metabolites of diazinon.

3.5.2 Mechanisms of Toxicity

Diazinon toxicity results predominantly from the inhibition of AChE in the central and peripheral nervous system. AChE is responsible for terminating the action of the neurotransmitter, acetylcholine, in the synapse of the pre- and postsynaptic nerve endings and in the neuromuscular junction. The action of acetylcholine does not persist long as it is hydrolyzed by AChE and rapidly removed. As an anticholinesterase organophosphate, diazinon inhibits AChE by reacting with the active site to form a stable phosphorylated complex incapable of destroying acetylcholine at the synaptic gutter between the pre- and postsynaptic nerve endings or neuromuscular junctions of skeletal muscles resulting in accumulation of acetylcholine at these sites. This leads to continuous or excessive stimulation of cholinergic fibers in the postganglionic parasympathetic nerve endings, neuromuscular junctions of the skeletal muscles, and cells of the central nervous system that results in hyperpolarization and receptor desensitization. These cholinergic actions involving end organs (heart, blood vessels, secretory glands) innervated by fibers in the postganglionic parasympathetic nerves result in muscarinic effects, which are manifested as miosis, excessive glandular secretions (salivation, lacrimation, rhinitis), nausea, urinary incontinence, vomiting, abdominal pain, diarrhea, bronchoconstriction or bronchospasm, increased bronchosecretion, vasodilation, bradycardia, and hypotension. Nicotinic effects are due to accumulation of acetylcholine at the skeletal muscle junctions and sympathetic preganglionic nerve endings. Nicotinic effects are manifested as muscular fasciculations, weakness, mydriasis, tachycardia, and hypertension. The central nervous system effects are due to accumulation of acetylcholine at various cortical, subcortical, and spinal levels (primarily in the cerebral cortex, hippocampus, and extrapyramidal motor system). The central nervous system effects are manifested as respiratory depression, anxiety, insomnia, headache, restlessness, tension, mental confusion, loss of concentration, apathy, drowsiness, ataxia, tremor, convulsion, and coma (Klaassen et al. 1986; Williams and Burson 1985). Although diazinon directly inhibits AChE, its oxidation product, diazoxon (Iverson et al. 1975; Yang et al. 1971) formed in the liver, is an even more potent inhibitor of the enzyme (Davies and Holub 1980a, 1980b; Enan et al. 1982; Harris et al. 1969; Rajendra et al. 1986; Takahashi et al. 1991).

The primary cause of death in acute diazinon poisoning is a depression of the neurons in the brainstem (medulla), collectively known as the respiratory center, resulting in loss of respiratory drive or, in the case of managed treatment, cardiac failure due to electrical impulse or beat conduction abnormalities in

cardiac muscles (fatal arrhythmias). Other effects, such as bronchoconstriction, excessive bronchial secretions, and paralysis of the respiratory muscles (intercostal muscles and diaphragm) may also contribute to respiratory insufficiency and death. Thus, death results from loss of respiratory drive and paralysis of the respiratory muscles, or cardiac failure, or both, with attendant asphyxia or cardiac arrest (Klaassen et al. 1986; Shankar 1967, 1978; Williams and Burson 1985).

Oxidative stress has been proposed as an additional mechanism of action for organophosphorus pesticides such as diazinon, particularly with respect to chronic effects on the central nervous system (Ray 1998) and developmental toxicity (Garry 2004; Roy et al. 2005). Akturk et al. (2006) noted increased malondialdehyde levels and increased activities of superoxide dismutase and catalase, indicators of increased lipid peroxidation, in myocardial cells of rats administered diazinon in a single 235 mg/kg oral dose. Giordano et al. (2007) assessed the role of oxidative stress in the neurotoxicity of diazinon and its oxygen analog (diazoxon) to cerebellar granule neurons from wild type and glutathione-deficient mice. Glutathione-deficient cells exhibit increased sensitivity to agents that increase oxidative stress. Cytotoxicity was significantly higher in neurons from glutathione-deficient mice and was antagonized by a variety of antioxidants. Manipulated depletion of glutathione in neurons from wild type mice resulted in increased cytotoxicity. Diazinon caused increased intracellular levels of reactive oxygen species and lipid peroxidation, the magnitudes of which were greatest in neurons from the glutathione-deficient mice. Diazinon increased cellular levels of oxidized glutathione without altering levels of reduced glutathione. Whereas diazinon-induced cytotoxicity was not altered by cholinergic antagonists, it was decreased by the calcium chelator BAPTA-AM. Collectively, these results indicate that diazinon cytotoxicity includes glutathione-modulated generation of reactive oxygen species and may include intracellular homeostasis of calcium.

3.5.3 Animal-to-Human Extrapolations

The general pharmacokinetic behavior of diazinon is similar in humans and laboratory animals. Available comparative data derive mainly from oral exposure. Following oral exposure, diazinon is rapidly absorbed, widely distributed, and metabolized to reactive intermediates and other metabolites, which are primarily quickly eliminated in the urine (see Section 3.4). Although animals and humans share these similarities, potential differences in pharmacokinetic behavior and biotransformation in blood and target tissues, particularly at exposure levels of toxicity concern, have not been extensively studied. Therefore, extrapolation from animals to humans includes an appreciable degree of uncertainty.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Information regarding the potential for diazinon-induced neuroendocrine effects is limited. No data are available regarding diazinon-induced hormonal effects. Results of available animal studies indicate that the reproductive system is not particularly sensitive to diazinon toxicity. No treatment-related morphological or functional effects on reproductive systems were seen in rats, mice, or rabbits administered diazinon orally at doses up to and including those eliciting maternal toxicity (Giknis 1989;

Green 1970; Harris and Holson 1981; Infurna and Arthur 1985; Spyker and Avery 1977). There was no histopathological evidence of diazinon-induced effects on reproductive organs of male or female rats or dogs chronically exposed to diazinon in the diet at doses up to and including those eliciting neurotoxic effects (Barnes 1988; Kirchner et al. 1991; Rudzki et al. 1991; Singh 1988). One study reported testicular atrophy and arrested spermatogenesis in 3 male dogs administered encapsulated diazinon at a dose level of 20 mg/kg/day for 8 months (Earl et al. 1971); however, one of these dogs died and there was significant weight loss, indicating that the testicular effects were likely secondary to primary neurotoxic effects. In another study, oral administration of diazinon to male albino rats at dose levels of 1.5 or 3 mg/kg/day for 65 days resulted in significantly decreased reproductive tissue weights, increased percentage of dead and morphologically abnormal spermatozoa, decreased plasma testosterone levels, and decreased fertility as assessed by conception rates of untreated females mated to diazinon-treated males (Abd El-Aziz et al. 1994).

Results of available *in vitro* assessments of diazinon estrogenicity indicate a potentially weak estrogenic effect at best. A positive estrogenic response was not elicited in a yeast two-hybrid assay at diazinon concentrations up to and including the highest concentration tested ($1x10^{-4}$ M) (Nishihara et al. 2000). Results of the E-CALUX assay indicated a weakly positive response at a diazinon concentration of $4.6x10^{-4}$ M (Kojima et al. (2005).

Collectively, these limited data indicate that the endocrine system may not be particularly sensitive to diazinon toxicity.

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).

It is not known whether children are more susceptible than adults to diazinon toxicity, although available human and animal data provide suggestive evidence of increased sensitivity during critical periods of development.

A single human study reported neurophysiological and neuropsychological deficits and delayed bone growth in young children exposed at home to a formulation of diazinon that was misused to control an infestation of fleas (Dahlgren et al. 2004). These results provide suggestive evidence that children may be particularly susceptible to diazinon toxicity during critical periods of neural and skeletal development.

Results of one animal study indicate that fetal exposure to low levels of diazinon may result in functional deficits that can only be detected by systemic behavioral evaluation (Spyker and Avery 1977). In the study, pregnant mice were exposed to diazinon (technical grade, purity not specified) in peanut butter at doses of 0, 0.18, or 9 mg/kg/day throughout gestation. When subjected to neuromuscular function tests (rod cling and inclined plane) as adults, the pups of both groups of diazinon-exposed dams exhibited endurance and coordination deficits. Offspring of the high-dose dams also displayed slower running speed in a Lashley III maze and reduced swimming endurance. Morphologically, focal abnormalities in the forebrain area, including dense aggregations of atypical chromatin-containing cells, were observed in the high-dose offspring. These neural dysfunctions and pathologies might occur either indirectly through diazinon impairment of placental transport of nutrients or maternal regulation of fetal growth, or directly via antagonism to cholinergic development of the fetus (Spyker and Avery 1977).

Results of subcutaneous injection studies indicate that critical periods of neurological development may be particularly sensitive to diazinon toxicity. Slotkin and coworkers (Jameson et al. 2007; Slotkin et al. 2006a, 2006b, 2007) reported evidence of diazinon-induced neurodevelopmental effects in the forebrain and brainstem of neonatal rats at dose levels near or below those eliciting significant cholinesterase inhibition, the most commonly-observed indicator of diazinon toxicity. In these studies, newborn rats were subcutaneously injected with diazinon on postnatal days 1–4 at doses ranging from 0.5 to 2 mg/kg/day.

The neurotoxicity of diazinon is dependent on its bioactivation via a cytochrome P-450 mediated desulfuration to the oxon form (Buratti et al. 2003). Age-related differences in production and regulation of enzymes involved in metabolism could conceivably result in age-related differences in susceptibility to diazinon toxicity. Age-related differences in regulation of selected P-450 isozymes have been demonstrated (Leeder and Kearns 1997). Age-related differences in relative amounts of plasma ChE,

RBC AChE, and neural AChE could potentially play roles in susceptibility to diazinon toxicity. Because plasma ChE binds diazinon, lesser amounts of plasma ChE would result in greater amounts of diazinon and its oxon available to interact with RBC and neural AChE, which could result in increased susceptibility to diazinon neurotoxicity. The same reasoning is plausible for RBC AChE concentrations. Decreased levels of RBC AChE could result in increased sensitivity to diazinon and its oxon via increased binding of neural AChE. Garcia-Lopez and Monteoliva (1988) demonstrated that RBC AChE activity in humans increases with age, starting at birth and exceeding 60 years of age.

In an *in vitro* assay designed to test the efficacy of rat liver and plasma to detoxify diazinon and its active metabolite, diazoxon, Padilla et al. (2004) demonstrated that liver and plasma from young rats possessed much less detoxification capability than adult tissues. Padilla et al. (2004) further demonstrated that oral administration of 75 mg diazinon/kg to 17-day-old rats resulted in 75% brain AChE inhibition, whereas the same dose to adult rats resulted in only 38% brain AChE inhibition. These results indicate that young rats may be more susceptible to the neurotoxic effects of diazinon and that age-related susceptibility may be at least partially associated with age-related differences in metabolic processes involved in detoxification.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the

body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to diazinon 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 diazinon 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 Diazinon

Diazinon is rapidly absorbed from the gastrointestinal tract and widely distributed throughout the body in both humans (Poklis et al. 1980) and animals (Janes et al. 1973; Mücke et al. 1970). Detection of diazinon in the blood and urine of occupationally-exposed workers may serve as a useful biomarker of very recent exposure to diazinon (Lu et al. 2006). No human or animal studies have reported the presence of unchanged diazinon in the urine following exposure. Traces of unchanged diazinon have been detected in animal feces following exposure (Mücke et al. 1970). Diazinon undergoes biotransformation to a variety of polar metabolites which have been detected in the urine and feces of animals. Urinary and fecal excretion of IMHP, DEP, and DETP have been reported following exposure of animals to diazinon (Iverson et al. 1975; Machin et al. 1975; Mount 1984; Mücke et al. 1970; Seiber et al. 1993; Yang et al. 1971). Both DEP and DETP have been detected in the urine of exposed insecticide applicators (Maizlish et al. 1987) and volunteers administered diazinon orally or dermally (Garfitt et al. 2002). Analysis of blood samples for the presence of these metabolites represents a potential means of assessing exposure; however, only IMHP is specific for diazinon. Analysis of urine samples for metabolic products provides

a noninvasive method for detecting exposure. As diazinon is rapidly metabolized and excreted from the body, urinary and fecal metabolite analysis is useful only in the evaluation of recent exposures. There are no reports of quantitative associations between metabolite levels and exposure to diazinon in humans. Therefore, these biomarkers are only indicative of exposure and are not useful for dosimetric analysis.

3.8.2 Biomarkers Used to Characterize Effects Caused by Diazinon

The major action resulting from human exposure to diazinon is the inhibition of cholinesterase activity (see Section 3.5 for discussion). Two pools of cholinesterases are present in human blood; RBC AChE and ChE. RBC AChE is identical to AChE present in neural tissue (the target of diazinon action) while plasma ChE has no known physiological function. Inhibition of both forms of cholinesterase has been associated with exposure to diazinon in humans (Coye et al. 1987; Soliman et al. 1982) and animals (Barnes 1988; Davies and Holub 1980a; EPA 1996, 2000a; Kirchner et al. 1991; Makhteshim-Agan 1989; Rudzki et al. 1991; Trutter 1991). Inhibition of plasma, RBC, or whole blood ChE may be used as a marker of exposure to diazinon. However, cholinesterase inhibition is a common action of anticholinesterase compounds such as organophosphates (which include diazinon) and carbamates. In addition, a wide variation in normal cholinesterase values exists in the general population, and there are no studies which report a quantitative association between cholinesterase activity levels and exposure to diazinon in humans. Thus, cholinesterase inhibition is not a specific biomarker of effect for diazinon exposure, but is indicative only of effect, and not useful for dosimetric analysis.

It should be noted that plasma ChE activity has been reported to be a more sensitive marker for diazinon exposure than RBC AChE activity (Endo et al. 1988; Hayes et al. 1980). In light of this, it has been suggested that in the absence of baseline values for cholinesterase activity, sequential postexposure cholinesterase analyses be used to confirm a diagnosis of organophosphate poisoning (Coye et al. 1987).

In combination with analysis of reductions in the level of cholinesterase activity, the manifestations of severe diazinon poisoning, clinically characterized by a collection of cholinergic signs and symptoms (which may include dizziness, fatigue, tachycardia or bradycardia, miosis, and vomiting) (Bichile et al. 1983; Dagli et al. 1981; Hata et al. 1986; Kabrawala et al. 1965; Klemmer et al. 1978; Reichert et al. 1977; Wadia et al. 1974; Wedin et al. 1984) are useful biomarkers of effect for identifying poisoned victims of diazinon. These manifestations are also not specific to diazinon but to anticholinesterase compounds (such as organophosphates and carbamates) in general.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Diazinon is one of many pesticides (organophosphates and carbamates) designed to act as AChE inhibitors. Significant occupational exposure to diazinon often occurs in workers who are exposed to other similarly-acting compounds. Neurotoxic effects in such individuals are the result of the cumulative dose and relative potency of each individual compound.

Although no studies were located that specifically assessed dermal absorption of diazinon in the presence of other chemicals, it is generally understood that a variety of solvents influence the rate and extent of absorption of organophosphate pesticides following dermal exposure.

A variety of chemicals may interfere with the toxicity of diazinon indirectly by influencing its metabolism through their actions on drug metabolizing enzymes. The duration and intensity of action of diazinon are largely determined by the speed at which it is metabolized in the body by the oxidative and hydrolytic liver enzymes. More than 200 drugs, insecticides, carcinogens, and other chemicals are known to induce the activity of liver microsomal drug-metabolizing enzymes. The characteristic biological actions of these chemicals are highly varied. Although there is no relationship between their actions or structures and their ability to induce enzymes, most of the inducers are lipid soluble at physiological pH. These inducers of the MFO system include the following classes of drugs: hypnotic and sedatives (barbiturates, ethanol); anesthetic gases (methoxyflurane, halothane); central nervous system stimulators (amphetamine); anticonvulsants (diphenylhydantoin); tranquilizers (meprobamate); antipsychotics (triflupromazine); hypoglycemic agents (carbutamide); anti-inflammatory agents (phenylbutazone); muscle relaxants (orphenadrine); analgesics (aspirin, morphine); antihistaminics (diphenhydramine); alkaloids (nicotine); insecticides (chlordane, DDT, BHC, aldrin, dieldrin, heptachlor epoxide, pyrethrins); steroid hormones (testosterone, progesterone, cortisone); and carcinogenic polycyclic aromatic hydrocarbons (3-methyl cholanthrene, 3,4-benzpyrene) (Klaassen et al. 1986; Williams and Burson 1985).

Thus, exposure to any of these enzyme inducers concurrent with or after exposure to diazinon may result in accelerated bioactivation to the more potent anticholinesterase diazoxon. The extent of toxicity mediated by this phenomenon is dependent on how fast diazoxon is hydrolyzed to less toxic metabolites, a process that is also accelerated by enzyme induction. Similarly, concurrent exposure to diazinon and MFO enzyme-inhibiting substances (e.g., carbon monoxide; ethylisocyanide; SKF 525A, halogenated alkanes, such as CCl_4; alkenes, such as vinyl chloride; and allelic and acetylenic derivatives) may increase

the toxicity of diazinon by decreasing the rate of the hydrolytic dealkylation and hydrolysis of both parent diazinon and activated diazinon (diazoxon) (Williams and Burson 1985). The balance between activation and detoxification determines the biological significance of these chemical interactions with diazinon.

Cimetidine, a histamine H_2 receptor agonist used to treat peptic ulcers and other gastric acid-related disorders, has been shown to potentiate the toxicity of diazinon. In a series of studies, Wu et al. (1996b, 1996c) demonstrated enhanced cholinergic signs, as well as increased brain AChE and carboxylesterase inhibition in diazinon-treated rats that had been pretreated with cimetidine. Significant decreases in total body clearance of diazinon and marked increases in the area under the plasma concentration-time curves following cimetidine treatment were also noted. *In vitro* assays demonstrated that cimetidine significantly decreased the hepatic metabolism of diazinon.

Diazinon exposure may interfere with the short-acting muscle relaxant, succinylcholine, used concurrently with anesthetics. The action of succinylcholine is terminated by means of its hydrolysis by plasma ChE (Klaassen et al. 1986). Since plasma ChE is strongly inhibited by diazinon (Davies and Holub 1980b; Klemmer et al. 1978), it is possible that concurrent exposure to diazinon may result in the prolongation of the action of succinylcholine leading to prolonged muscular paralysis.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

The magnitude of diazinon toxicity, like the toxicity of any xenobiotic, is affected by the rate of its metabolic biotransformation to both more and less toxic substances (Klaassen et al. 1986). The newborn of several animal species, including humans, have a reduced ability to metabolize xenobiotics. Available animal data indicate that developing animals may be particularly sensitive to diazinon neurotoxicity (Spyker and Avery 1977). However, the effect of decreased metabolism on diazinon-induced neurotoxicity has not been demonstrated.

Studies on experimental animals showed that starvation depressed liver microsomal enzyme (P-450) activity due to actual loss of the enzyme protein (Boyd and Carsky 1969). Thus, dietary protein deficiency could potentially alter diazinon toxicity by diminishing its metabolism in the liver. Hereditary factors may also contribute to population sensitivity to diazinon. Atypical plasma ChE with low activity is present in a small percentage of the human population. This altered enzyme is the result of a hereditary factor with 0.04% occurrence in the population. Since plasma ChE is strongly inhibited by diazinon (Davies and Holub 1980b; Klemmer et al. 1978), it is expected that individuals who have atypical ChE (or low plasma ChE activity) will be unusually sensitive to the muscle relaxant succinylcholine (Klaassen et al. 1986) and may suffer prolonged muscle paralysis if administered succinylcholine while exposed to diazinon. Congenital low plasma ChE activity may also increase subpopulation sensitivity to diazinon exposure. This is because, after exposure, plasma ChE acts as a depot for diazinon due to its strong affinity for the substance (Davies and Holub 1980b; Klemmer et al. 1978), thus decreasing the availability of the diazinon dose to the target (neuromuscular tissue) of diazinon toxicity in the population with normal plasma ChE levels. In individuals with congenital low plasma ChE activity, less diazinon is bound in the blood and more unbound diazinon is in circulation to reach the target of diazinon toxicity (neuromuscular tissue). Ueyama et al. (2007) demonstrated significantly increased ChE and RBC and brain AChE inhibition in streptozotocin-induced diabetic rats compared to normal rats, an indication that diabetics may be more susceptible to OP-induced neurotoxicity.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to diazinon. 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 diazinon. 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 diazinon:

Clark RF. 2002. Insecticides: Organic phosphorus compounds and carbamates. In: Goldfrank LR, Flomenbaum NE, Lewin NA, et al. eds. Goldfrank's toxicologic emergencies. 7th ed. New York, NY: Mc-Graw-Hill Medical Publishing Division, 1346-1360.

Carlton FB, Simpson WM, Haddad LM. 1998. The organophosphates and other insecticides. In: Haddad LM, Shannon MW, Winchester JF, eds. Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: WB Saunders Company, 836-845.

Osmundson M. 1998. Insecticides and pesticides. In: Viccellio P, Bania T, Brent J, et al., eds. Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers, 401-413.

3.11.1 Reducing Peak Absorption Following Exposure

The following information was extracted from the texts listed above; specific chapters were written by Clark (2002), Carlton et al. (1998), and Osmundson (1998), respectively. Following dermal contamination with organophosphates, most texts recommend washing the skin with copious amounts of soap and water, which may be followed by a second washing with ethyl alcohol to remove the contaminant from the skin. However, it should be noted that ethyl alcohol may also enhance the dermal absorption of some chemicals as evidenced by its function as an enhancer in some transdermal patches. Contaminated clothing, including leather garments, should be destroyed. After oral ingestion, activated charcoal is recommended for many organophosphates, although Carlton et al. (1998) note that it may lack efficiency with some organophosphates. Osmundson (1998) points out that Ipecac should not be used for organophosphate poisoning. Cathartics may be unnecessary as intestinal motility is greatly increased. Gastric lavage may be performed with care to prevent aspiration, as organic solvent vehicles may precipitate pneumonitis. Treatment of inhaled organophosphates is mostly supportive as respiratory distress is a common effect of poisoning; intubation may be necessary to facilitate control of secretions.

3.11.2 Reducing Body Burden

Diazinon is rapidly metabolized, with an estimated mammalian biological half-life of 12–15 hours (Iverson et al. 1975; Mücke et al. 1970). Consequently, efforts at reducing body burdens of poisoned persons may not be critical to the outcome. Dialysis and hemoperfusion are not indicated in organophosphate poisonings because of the extensive tissue distribution of the absorbed doses (Mücke et al. 1970; Poklis et al. 1980).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The following information has been extracted from the texts listed above. Administration of atropine and pralidoxime (2-PAM) seems to be a universally accepted treatment for organophosphate poisoning. It should be mentioned, however, that glycopyrrolate, a quaternary ammonium compound, has also been used instead of atropine (Bardin and Van Eeden 1990). Unlike atropine, glycopyrrolate does not cross the blood-brain barrier and, therefore, has fewer central nervous system effects. Atropine is a competitive antagonist at muscarinic receptor sites and since it crosses the blood-brain barrier, it also treats the central nervous system effects. Atropine is particularly helpful in drying excessive secretions especially from the

tracheobronchial tree. Atropine does not antagonize nicotinic effects; therefore, 2-PAM is needed for treatment of muscle weakness and respiratory depression. Most texts recommend an initial dose of 1–2 mg for an adult and 0.05 mg/kg for children, preferably by the intravenous route. This may be repeated every 15–30 minutes until signs of atropinization occur. 2-PAM is a quaternary amine oxime that can reverse the phosphorylation of AChE and thereby restore activity. It may also prevent continued toxicity by detoxifying the organophosphate molecule and has an anticholinergic effect (Carlton et al. 1998). 2-PAM and other oximes function by nucleophilic attack on the phosphorylated enzyme; the oxime-phosphonate is then split off, leaving the regenerated enzyme. 2-PAM should be administered as soon as the diagnosis is made. The initial dose is normally 1–2 g for adults and 25–50 mg/kg for children administered intravenously over 30–60 minutes. The dose can be repeated in 1 hour and then every 8–12 hours until clinical signs have diminished and the patient does not require atropine. Some patients may require higher doses or multiple doses, as enzyme regeneration depends on plasma levels of the organophosphate. A 2-PAM serum level of 4 µg/L is suggested as the minimum therapeutic threshold. 2-PAM is considered a very safe drug with few side effects.

3.12 ADEQUACY OF THE DATABASE

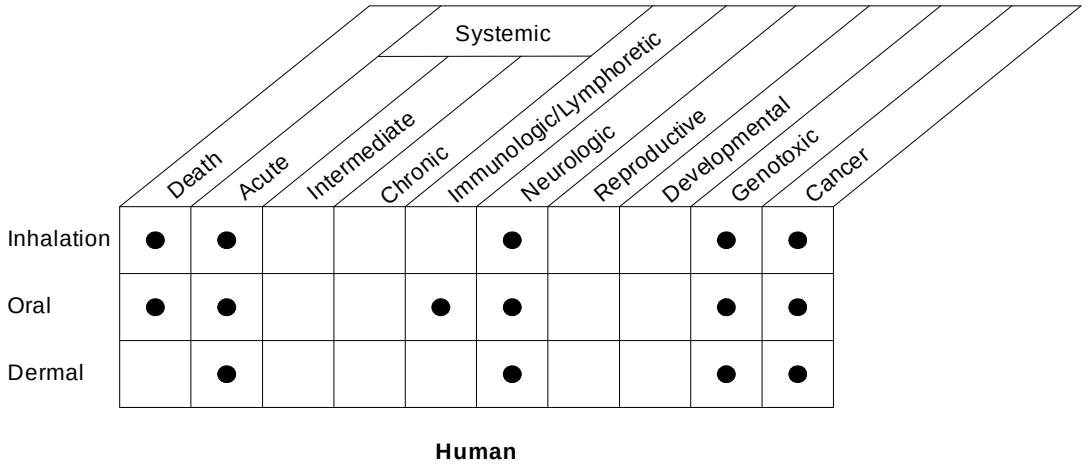
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of diazinon is available. Where adequate information is not available, 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 diazinon.

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.

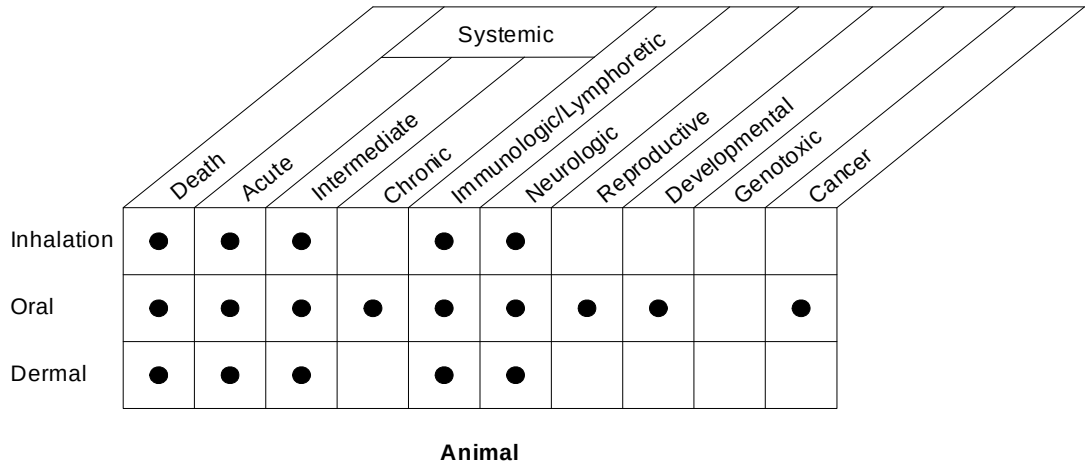
3.12.1 Existing Information on Health Effects of Diazinon

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to diazinon are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of diazinon. Each dot in the figure indicates that one or more studies

Figure 3-5. Existing Information on Health Effects of Diazinon



Human



Animal

● Existing 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.

Most of the literature reviewed concerning the health effects of diazinon in humans described case reports of individuals or groups of individuals exposed either occupationally or in the home following intentional poisoning attempts or otherwise accidental misuse of diazinon or diazinon-containing solutions. The predominant route of occupational exposure is believed to be dermal while that for accidental or intentional exposure in the home is oral, although some inhalation exposures were reported. Thus, Figure 3-5 reflects that information exists for all three routes of exposure. However, all of these reports are limited because of the possibility of concurrent or sequential exposure to other potentially toxic substances present in the environment (workplace or home), such as other insecticides, or present as components of diazinon-containing formulations. In all cases, accurate information regarding levels and duration of exposure were not presented in these reports. Further, the health effects of human acute exposure to diazinon are much more fully characterized than those associated with intermediate and chronic exposures.

Information regarding the health effects of diazinon following ingestion in laboratory animals is substantial, but less information is available on the effects of inhalation and dermal exposures (see Figure 3-5). Furthermore, the health effects of acute- and intermediate-duration exposures to diazinon are more fully characterized than those associated with chronic-duration exposures. The available information indicates that diazinon is a toxic substance to all species of experimental animals, deriving its toxicity from AChE inhibition.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Information is available on the effects of acute-duration exposures in humans and experimental animals (rats and mice). The available human data consist primarily of studies of cholinergic (neurological) reactions resulting from AChE inhibition. Effects noted include respiratory, cardiovascular, hematological, kidney, liver, gastrointestinal tract, endocrine, neurological, and

immunologic/lymphoreticular system toxicity (Balani et al. 1968; Bichile et al. 1983; Dagli et al. 1981; DePalma et al. 1970; Hata et al. 1986; Kabrawala et al. 1965; Klemmer et al. 1978; Lee 1989; Limaye 1966; Lisi et al. 1987; Matsushita and Aoyama 1981; Poklis et al. 1980; Shankar 1967; Wadia et al. 1974; Wecker et al. 1985; Wedin et al. 1984; Weizman and Sofer 1992). The type of information available in animals includes LD_{50} values (Boyd and Carsky 1969; Enan et al. 1982; Gaines 1960, 1969; Harris et al. 1969) and cholinergic (neurological) reactions resulting from AChE inhibition. Effects noted include respiratory, gastrointestinal, hematological, liver, kidney, immunologic/lymphoreticular, and neurological toxicity (Boyd and Carsky 1969; Enan et al. 1982; Lox 1983; Mihara et al. 1981). Thus, while the acute effects of diazinon inhalation and oral exposure in humans are well-characterized and stem principally from AChE inhibition, the diazinon exposure levels at which these effects begin to occur are usually not known. Available animal studies provide adequate insight into the AChE inhibiting action of diazinon in acute oral exposures. Results of one study (Davies and Holub 1980a) serve as the basis for deriving an acute-duration oral MRL for diazinon. Available acute-duration inhalation data in animals are restricted to a single report of nasal discharge, polyuria, decreased activity, and salivation in a group of five rats exposed to a diazinon aerosol at a concentration of 2,330 mg/m^3. This study was not suitable for MRL derivation because it included a single exposure level at which serious effects were observed and no supporting data were available. Quantitative acute-duration inhalation toxicity data for humans and laboratory animals are needed to assist in the derivation of an acute-duration inhalation MRL for the protection of populations, especially those surrounding hazardous waste sites or establishments where wastes containing diazinon are released into the air or water, and those that are occupationally exposed to high levels of diazinon for brief periods.

Intermediate-Duration Exposure. Information is available on the effects of intermediate-duration exposures in humans and experimental animals (rats, dogs, pigs). The type of information available includes studies of cardiovascular, gastrointestinal, hematological, hepatic, musculoskeletal, renal, body weight, immunologic/lymphoreticular, and neurological effects (Alluwaimi and Hussein 2007; Anthony et al. 1986; Davies and Holub 1980a, 1980b; Earl et al. 1971; Enan et al. 1982; Kalender et al. 2005, 2006; Lox and Davis 1983; Ogutcu et al. 2006). Data from these studies sufficiently demonstrate the cholinergic effects of diazinon. The adverse effects reported in humans and laboratory animals following exposure via inhalation, oral, or dermal routes are predominately cholinergic responses deriving from inhibition of AChE. An intermediate-duration inhalation MRL was derived for diazinon based on RBC AChE inhibition in rats (Hartman 1990). An intermediate-duration oral MRL was derived based on RBC AChE inhibition in orally-exposed rats (Davies and Holub 1980a). Further information on the dermal toxicity and toxicokinetics for all routes in both humans and laboratory animals would be helpful for use

in additional assessment of intermediate-duration exposure, especially for persons near hazardous waste sites or establishments where wastes containing diazinon are released, or near agricultural establishments where diazinon is used regularly.

Chronic-Duration Exposure and Cancer. No adequate epidemiological studies are available regarding the potential carcinogenicity or systemic toxicity of diazinon resulting from chronic exposure in humans. Two adequate studies have been conducted with rats and mice orally exposed to diazinon (NCI 1979). While not designed as a cancer bioassay, in a study where rats (groups of 20–30) were orally exposed to diazinon for 98 weeks, histopathology of some 30–40 different tissues showed no treatment-related increase in neoplasms (Kirchner et al. 1991). This rat study included sufficient information regarding AChE inhibition to justify the derivation of a chronic-duration oral MRL for diazinon. A 52-week oral toxicity study in dogs is available as well (Rudzki et al. 1991). No chronic inhalation MRL was calculated for diazinon because no studies for this route are available. Toxicity and toxicokinetic data from well-conducted inhalation studies in both humans and laboratory animals would be helpful in developing a chronic-duration inhalation MRL for the protection of populations, especially those surrounding hazardous waste sites or establishments where wastes containing diazinon are released into the air or water, and those occupationally exposed to diazinon for long periods of time.

Epidemiological studies available on diazinon are inadequate for assessing the carcinogenic potential of this chemical substance. The results from these studies are confounded by either concurrent or sequential (or both) exposures to other potentially toxic substances, mainly other insecticides (Cantor et al. 1992; Davis et al. 1993; Morris et al. 1986), although cancers in several tissue types (unspecified type of childhood brain cancer, non-Hodgkin's lymphoma, multiple myeloma) were identified in these chronic human exposure studies(presumed to involve multiple concurrent routes of exposure). In adequate cancer oral bioassays conducted in rats and mice, the NCI (1979) concluded that diazinon is not carcinogenic in these species under the conditions of the bioassays. Chronic inhalation and dermal bioassays would be helpful to determine whether long-term inhalation or dermal exposures in populations, especially those surrounding hazardous waste sites or establishments where wastes containing diazinon are released into the air or water, and those occupationally exposed to diazinon for long periods of time, are at risk of developing cancers.

Genotoxicity. Chronic occupational exposure to multiple insecticides, including diazinon, has been associated with an increased incidence of chromosomal aberration and increased sister chromatid exchange in peripheral blood lymphocytes of these individuals (de Ferrari et al. 1991; Kiraly et al. 1979;

See et al. 1990). The results from these studies are confounded by either concurrent or sequential (or both) exposures to other unknown toxic substances, mainly other insecticides, that may be genotoxic. Significantly increased sister chromatid exchanges were noted in peripheral blood lymphocytes from a group of volunteers following exposure to diazinon in a sheep-dip formulation (Hatjian et al. 2000). However, the specific role of diazinon in the observed effect could not be determined because the sheep-dip formulation contained other ingredients as well.

Limited information is available regarding the genotoxicity of diazinon in nonhuman species *in vivo*. Diazinon did not induce sister chromatid exchanges in the bone marrow of mice administered 100 mg/kg diazinon by gavage (EPA 1990). Diazinon induced mutations in a wing SMART of *Drosophila melanogaster* (Çakir and Sarikaya 2005).

The results of *in vitro* tests in a variety of test systems (predominantly microbial assays) are equivocal. Diazinon was positive for gene mutations in one test using the *S. typhimurium* mutagenicity or reverse mutation assay with metabolic activation (Wong et al. 1989) and in the mouse lymphoma cell forward mutation assay without metabolic activation (McGregor et al. 1988). The compound was also positive for chromosomal aberrations in Chinese hamster cells with metabolic activation (Matsuoka et al. 1979). In contrast, evaluations for genetic mutation activity in the *S. typhimurium* mutagenicity or reverse mutation assay (Marshall et al. 1976) and in the *rec*-assay utilizing strains of *B. subtilis* (Shirasu et al. 1976) without metabolic activation, and in tests for sister chromatid exchange in Chinese hamster cells, both with and without metabolic activation (Chen et al. 1982), and for chromosomal aberrations in human peripheral blood lymphocytes (Lopez et al. 1986), were all negative. A full battery of *in vivo* tests in animals and additional *in vitro* tests in microbial systems for all genetic end points is necessary for the determination of the genetic toxicity potential of diazinon.

Reproductive Toxicity. No information was located on the reproductive effects of diazinon exposure in humans. Limited data are available regarding diazinon-induced reproductive effects in animals. Increased litter size was reported in one study of diazinon-treated rats (Green 1970), although a second rat study reported significant reduction in litter size at oral maternal diazinon doses of 0.18 and 9 mg/kg/day (Spyker and Avery 1977). Diazinon-induced adverse effects on reproductive tissue weights, sperm quality, and fertility were noted in orally-exposed male rats (Abd El-Aziz et al. 1994). Testicular atrophy and arrested spermatogenesis were noted in dogs administered diazinon orally at doses ≥10 mg/kg/day for up to 8 months (Earl et al. 1971). No adverse effects on reproduction were observed in four generations of rats following oral administration of diazinon to female rats from each generation for 60 days prior to

weaning (Green 1970). No gross or histological evidence of treatment-related damage to reproductive tissues was observed in rats receiving diazinon in the diet for 13 weeks (Singh 1988)or 98 weeks (Kirchner et al. 1991), or in dogs exposed for 13 weeks (Barnes 1988). A well-designed multigenerational reproductive toxicity rat or mouse study is needed to more adequately assess the potential for diazinon to cause reproductive toxicity in humans.

Developmental Toxicity. Information regarding the developmental effects in humans from exposure to diazinon was not located. Four of the located studies in laboratory animals did not find any significant developmental effects in the rats, mice, hamsters, and rabbits tested (Barnett et al. 1980; Green 1970; Robens 1969; Spyker and Avery 1977). In two of these studies, marked reduction in rat pup birth weight and continued significant retardation in growth rate (Green 1970), or significantly elevated mortality in rat pups at weaning (Barnett et al. 1980) were reported. It has been suggested that the effects reported for pups derive from diazinon impairment of placental transport of nutrients or maternal regulation of fetal growth, or directly via antagonism to cholinergic development of the fetus (Spyker and Avery 1977). Collectively, the results of available studies for diazinon indicate that the compound is not of particular developmental toxicity concern at exposure levels lower than those resulting in maternal neurotoxicity, although additional neurodevelopmental toxicity studies could be designed to more critically test the neurodevelopmental toxicity potential.

Immunotoxicity. Autopsy reports in which the victims were exposed to high acute doses of diazinon described damage to lymphoreticular organs (spleen, thymus) (Limaye 1966; Poklis et al. 1980). One human study reported allergic interaction between the fungicide benomyl and diazinon from prolonged dermal contact with diazinon (Matsushita and Aoyama 1981). Several oral animal studies also reported damage to immune structures in rats and dogs. Rats exhibited reduced spleen weight, splenic red pulp contraction, reduced thymus weight, and thymic atrophy ranging from minor to near total loss of thymocytes following acute exposure to moderate doses of diazinon (Boyd and Carsky 1969). Dose-related splenic degeneration after 232 days of diazinon exposure was also reported in 1/3 diazinon-treated dogs (Earl et al. 1971). The splenic atrophy reported in this study may be a result of the generalized emaciated condition of the dog due to diarrhea, emesis, and anorexia. Exposure of guinea pigs in a dermal sensitization study resulted in allergic interaction between the fungicide benomyl and diazinon (Matsushita and Aoyama 1981). Dermal application of diazinon induced delayed contact hypersensitivity at both 24 and 48 hours after challenge in the guinea pig maximization test (Matsushita et al. 1985). Oral administration of diazinon to mice resulted in increased levels of interleukin-10 in selected splenic lymphocyte subpopulations and decreased levels of interferon-γ in B cells (Alluwaimi and Hussein 2007).

These results indicate a diazinon-induced effect on cytokines involved in the regulation of cellular and humoral responses. No gross or histological evidence of treatment-related damage to the spleen or thymus was observed in rats receiving diazinon from feed for 13 weeks (Singh 1988) or 98 weeks (Kirchner et al. 1991), or dogs receiving diazinon in the diet for 13 weeks (Barnes 1988) or 52 weeks (Rudzki et al. 1991). Based on equivocal results from available animal studies, additional human and animal data would be helpful in defining the immunologic/lymphoreticular injury potential of diazinon in humans.

Neurotoxicity. Available evidence shows that diazinon exposure in humans results in the inhibition of neural AChE (Coye et al. 1987; Davies and Holub 1980a, 1980b; Enan et al. 1982; Harris et al. 1969; Rajendra et al. 1986; Takahashi et al. 1991; Wecker et al. 1985). Severe inhibition of this enzyme results in accumulation of acetylcholine at its sites of action and excessive or interminable stimulation of both sympathetic and parasympathetic cholinergic receptors leading to muscarinic and nicotinic effects. Clinical signs of diazinon-induced neurotoxicity include muscular fasciculations, weakness, and paralysis; mydriasis; tachycardia; hypertension; miosis; excessive glandular secretions (salivation, lacrimation, rhinitis); nausea; urinary incontinence; vomiting; abdominal pain; diarrhea; bronchoconstriction or bronchospasm; increased bronchosecretion; vasodilation; bradycardia; hypotension; respiratory depression; anxiety; insomnia; headache; restlessness; tension; mental confusion; loss of concentration; apathy; drowsiness; ataxia; tremor; convulsion; and coma (Adlakha et al. 1988; Bichile et al. 1983; Coye et al. 1987; Kabrawala et al. 1965; Klaassen et al. 1986; Klemmer et al. 1978; Maizlish et al. 1987; Rayner et al. 1972; Shankar 1967, 1978; Williams and Burson 1985). These neurological effects have also been reported in diazinon-treated rats (Boyd and Carsky 1969; Earl et al. 1971). The current information from human and laboratory animal studies provides sufficient demonstration that the nervous system is the primary target of diazinon poisoning. The database of animal information for acute-, intermediate-, and chronic-duration oral exposure to diazinon is sufficiently characterized to allow the derivation of acute-, intermediate-, and chronic-duration oral MRLs. Health effects following intermediate-duration inhalation exposure to diazinon have been sufficiently characterized to allow the derivation of an intermediate-duration inhalation MRL. However data are lacking for acute- and chronic-duration inhalation exposure. Additional animal studies to assess inhalation exposure for acute- and chronic-duration exposure to diazinon should be designed to allow for the derivation of inhalation MRLs for these exposure durations as well. Information regarding health effects following dermal exposure are limited (EPA 1990; Lee 1989), but indicate that dermal exposure to relatively high doses of diazinon would result in neurological effects similar to those elicited from oral or inhalation exposure.

Epidemiological and Human Dosimetry Studies. Information on the health effects of diazinon in humans is derived from case reports of accidental or intentional exposure to diazinon, epidemiological studies, and controlled exposure studies (Adlakha et al. 1988; Alavanja et al. 2004; Beane Freeman et al. 2005; Bichile et al. 1983; Cantor et al. 1992; Dagli et al. 1981; Dahlgren et al. 2004; Davis et al. 1993; EPA 2000a, 2001; Hata et al. 1986; Kabrawala et al. 1965; Klemmer et al. 1978; Maizlish et al. 1987; Morris et al. 1986; Rayner et al. 1972; Reichert et al. 1977; Richter et al. 1992; Schenker et al. 1992; Shankar 1967, 1978; Soliman et al. 1982; Wadia et al. 1974; Wedin et al. 1984). The most likely identifiable subpopulations exposed to diazinon are pesticide applicators, farm workers, and individuals involved in the production of diazinon, since diazinon is no longer registered for use in residential pesticides in the United States (EPA 2004b). Well-designed epidemiological studies of exposed workers are needed. The nervous system is a known target of acute exposure, but little is known regarding possible long-term effects of acute exposure to high levels of diazinon or longer-term exposure at relatively low exposure levels. Additional epidemiological studies should assess the potential effects of such exposure scenarios.

Biomarkers of Exposure and Effect.

Exposure. Diazinon is rapidly absorbed from the gastrointestinal tract and widely distributed throughout the body in both humans (Poklis et al. 1980) and animals (Janes et al. 1973; Mücke et al. 1970). Potential biomarkers of exposure to diazinon include parent compound and metabolites of diazinon such as IMHP, DEP, and DETP. However neither parent compound nor metabolites of diazinon have been demonstrated to represent quantitative indicators of diazinon exposure levels. No human or animal studies have reported the presence of unchanged diazinon in the urine following exposure, although traces of unchanged diazinon have been detected in animal feces following exposure (Mücke et al. 1970). Urinary and fecal excretion of IMHP, DEP, and DETP have been reported following oral exposure of animals to diazinon (Iverson et al. 1975; Machin et al. 1975; Mount 1984; Mücke et al. 1970; Seiber et al. 1993; Yang et al. 1971). Both DEP and DETP have been detected in the urine of exposed insecticide applicators (Maizlish et al. 1987) and volunteers administered diazinon orally or dermally (Garfitt et al. 2002). Although analysis of urine samples for the presence of these metabolites represents a potential means of assessing recent human exposure to diazinon, DEP and DETP can originate from exposure to other organophosphorus compounds and, therefore, are not specific for diazinon exposure. Further studies designed to refine the identification of metabolites specific to diazinon and provide dosimetric data will be useful in the search for a more dependable biomarker of diazinon exposure.

The development of recent analytical techniques allows for the simultaneous detection of numerous biomolecules, thus facilitating complete description of the genome for a particular organism (genomics). These techniques can be applied to analysis of multiple gene transcripts (transcriptomics), proteins (proteomics), and metabolites (metabolomics). The application of these techniques to conventional toxicology is known as toxicogenomics. Although toxicogenomic data are not presently available for diazinon, such data could eventually lead to a more complete understanding of pharmacokinetic pathways involved in diazinon toxicity and might possibly elucidate particular biomarkers of exposure.

Effect. The major action resulting from human exposure to diazinon is the inhibition of AChE (Coye et al. 1987; Davies and Holub 1980a, 1980b; Enan et al. 1982; Harris et al. 1969; Rajendra et al. 1986; Takahashi et al. 1991; Wecker et al. 1985). Two pools of cholinesterases are present in human blood: RBC AChE and plasma ChE. RBC AChE is identical to AChE present in neuromuscular tissue (the target of diazinon action). Inhibition of both forms of cholinesterase has been associated with exposure to diazinon in humans (Coye et al. 1987; Soliman et al. 1982) and animals. While plasma ChE has no known physiological function, available data indicate that plasma ChE activity is a more sensitive marker for diazinon exposure than RBC AChE activity (Endo et al. 1988; Hayes et al. 1980). Therefore, future studies that provide qualitative and dosimetric information regarding diazinon exposure and plasma ChE inhibition may provide a useful biomarker of effect for diazinon (or other anticholinesterase compounds) exposure. Currently, no effect specific to diazinon exposure has been identified by any study. Future studies designed to provide such information would be useful in identifying exposure to diazinon.

Absorption, Distribution, Metabolism, and Excretion. No studies were located regarding distribution and metabolism of diazinon after inhalation or dermal exposure in humans or animals, or regarding the excretion of diazinon after dermal exposure in animals. Diazinon was detected in several tissues from a woman who had ingested a lethal amount of a diazinon formulation, indicating rapid gastrointestinal tract absorption (Poklis et al. 1980). Rapid and extensive absorption was noted following the ingestion of a 0.011 mg/kg dose of diazinon by a group of five volunteers (Garfitt et al. 2002). Results of animal studies confirm the rapid absorption of diazinon following oral administration (Abdelsalam and Ford 1986; Iverson et al. 1975; Janes et al. 1973; Machin et al. 1971, 1974; Mücke et al. 1970; Wu et al. 1996a). Dermal absorption of diazinon has also been demonstrated in humans (Garfitt et al. 2002; Wester et al. 1993). Animal studies confirm the observation of rapid, widespread distribution of absorbed diazinon (Abdelsalam and Ford 1986; Janes et al. 1973; Machin et al. 1971, 1974; Mücke et al. 1970). Both human and animal data demonstrate rapid metabolism of diazinon and its oxon to DEP, DETP, and IMHP, which are predominantly excreted in the urine (Garfitt et al. 2002; Klemmer et al.

1978; Mücke et al. 1970; Poklis et al. 1980; Wester et al. 1993; Wu et al. 1996a). Additional studies designed to quantify the toxicokinetics of diazinon following inhalation, oral, and dermal exposure in humans and animals would be useful. Dermal exposure studies could be designed to assess the extent of diazinon degradation on the skin prior to absorption and the relative dermal penetrability of diazinon breakdown products.

Comparative Toxicokinetics. A PBPK/PD model has been developed to predict both pharmacokinetic disposition of diazinon and metabolites and pharmacodynamic effect (esterase activity inhibition) for diazoxon in target tissues of rats and humans for multiple routes of exposure (Poet et al. 2004). The model structure is identical for both rats and humans, with species-specific parameter values used for physiological volumes and flow rates and model-optimized values used for oral absorption. The model was evaluated for simulating oral, intravenous, and intraperitoneal doses in rats ranging from 15 to 100 mg/kg. For humans, it was evaluated for a single oral dose level of 11 µg/kg and a dermal dose of 4 mg/kg. In humans, the model predicts urine levels of diazinon metabolites from oral and dermal exposures that are very similar to observations; however, the ability of the model to accurately simulate levels of diazinon and diazoxon and levels of esterase inhibition in human target tissues is uncertain due to the lack of human data to validate these endpoints. Therefore, the model was not used for MRL derivation. Additional human data regarding blood and RBC diazinon and diazoxon levels would serve to reduce uncertainty of the human model predictions. Comparative human and rat pharmacokinetic studies of diazinon could also provide valuable species-specific pharmacokinetic data and reduce uncertainty of PBPK model predictions.

Methods for Reducing Toxic Effects. Procedures used to limit absorption and to interfere with the mechanism of action of organophosphates, including diazinon, following acute exposure have been adequately described (Carlton et al. 1998; Clark 2002; Osmundson 1998). However, methods for reducing toxicity following long-term, low-level exposure are lacking, and would be needed if potential health effects from long-term, low-level exposure to diazinon are identified.

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

It is not known whether children are more susceptible than adults to diazinon toxicity. A single human study reported neurophysiological and neuropsychological deficits and delayed bone growth in young

children exposed at home to a formulation of diazinon that was misused to control an infestation of fleas (Dahlgren et al. 2004). These results provide suggestive evidence that children may be particularly susceptible to diazinon toxicity during critical periods of neural and skeletal development. Results of one animal study indicated that fetal exposure to low levels of diazinon may result in functional deficits that can only be detected by systemic behavioral evaluation (Spyker and Avery 1977). Results of subcutaneous injection studies indicate that critical periods of neurological development may be particularly sensitive to diazinon toxicity (Jameson et al. 2007; Slotkin et al. 2006a, 2006b, 2007). Young rats appear to be more susceptible than adult rats to diazinon-induced brain AChE inhibition, which may be at least partially due to decreased detoxification capability in the young rats (Padilla et al. 2004). Additional animal studies should be designed to support initial findings of age-related differences in susceptibility to diazinon toxicity.

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

3.12.3 Ongoing Studies

Three ongoing studies pertaining to diazinon were located in a search of the Federal Research in Progress database (FEDRIP 2006).

Dr. L. Costa of Fred Hutchinson Cancer Research Center, Seattle, Washington is investigating relationships between PON1 polymorphism and diazinon and diazoxon metabolism using a physiologically-based kinetic model.

Dr. J. Seifert of the University of Hawaii, Honolulu, Hawaii is searching for changes in rat liver proteins that may be linked to diazinon-induced alterations in blood glucose concentrations and the metabolism of l-tryptophan at intraperitoneally-injected doses of diazinon that are clearly neurotoxic.

Dr. B. Wilson of the University of California, Davis, California is using organophosphates, including diazinon, to develop biomarkers of exposure and to study the molecular and cellular mechanisms of toxicity as part of a more wide-ranging project.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

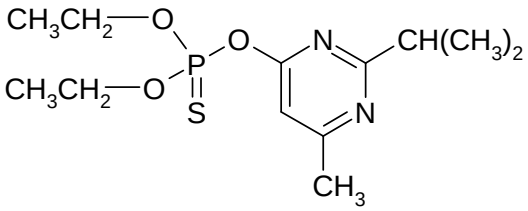
Information regarding the chemical identity of diazinon is located in Table 4-1.

Diazinon is manufactured in the United States and formulated as granules, a wettable powder, an emulsifiable solution, a dust, a seed dressing, or a mixed formulation with other insecticides. Manufacture of diazinon for indoor use products in the United States was discontinued as of March 1, 2001, and manufacture of non-agricultural outdoor use products was discontinued as of June 30, 2003 (HSDB 2008; WHO 1998).

4.2 PHYSICAL AND CHEMICAL PROPERTIES

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

Table 4-1. Chemical Identity of Diazinon

Characteristic	Information	Reference
Chemical name	O,O-Diethyl O-(2-isopropyl-6-methyl-4-pyrimidinyl) phosphorothioate	HSDB 2008
Synonyms(s)	O,O-Diethyl-O-(2-isopropyl-4-methyl-6-pyrimidinyl) phosphorothioate; O,O-diethyl-O-6-methyl-2-isopropyl-4-pyrimidinyl] phosphorothioate; others	HSDB 2008
Registered trade name(s)	Diazinon; Alfa-tox; Basudin; Diazol; Gardentox; Knox-Out; Spectracide; others	HSDB 2008
Chemical formula	$C_{12}H_{21}N_2O_3PS$	HSDB 2008
Chemical structure		Kappers et al. 2001
Identification numbers:		
CAS registry	333-41-5	HSDB 2008
NIOSH RTECS	TF 3325000	NIOSH 2006
EPA hazardous waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	UN 2783 Organophosphorouspesticides; UN 2784 Organophosphorouspesticides; UN 3017 Organophosphorouspesticides; UN 3018 Organophosphorouspesticides; IM06.1 Organophosphorouspesticides; solid; IMO3.0 Organophosphorouspesticides; liquid	HSDB 2008
HSDB	303	HSDB 2008
NCI	CO 8673	HSDB 2008

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

Table 4-2. Physical and Chemical Properties of Diazinon

Property	Information	Reference
Molecular weight	304.35	HSDB 2008
Color	Colorless	HSDB 2008
Physical state	Liquid	HSDB 2008
Melting point	No data	HSDB 2008
Boiling point	83–84 °C at $2x10^{-3}$ mm Hg; decomposes at >120 °C	O'Neil et al. 2001
Density:		
at 20 °C/4 °C	1.116–1.118 g/mL	HSDB 2008
Odor	Faint ester-like	HSDB 2008
Odor threshold:		
Water	No data	
Air	No data	HSDB 2006
Taste threshold	No data	
Solubility:		
Water at 20 °C	0.004% (40 mg/L)	HSDB 2008
Organic solvent(s)	Miscible with petroleum ether, alcohols, ether, cyclohexane, benzene and similar hydrocarbons	HSDB 2008
Partition coefficients:		
Log K_{ow}	3.81	HSDB 2008
Log K_{oc}	1.602–2.635, average for three soils, 2.281	HSDB 2008
Vapor pressure		
at 20 °C	$9.01x10^{-5}$ mm Hg	HSDB 2008
at 40 °C[b]	$1.1x10^{-3}$ mm Hg	O'Neil et al. 2001
Henry's law constant	$1.17x10^{-7}$ atm-m^3/mol	
Autoignition temperature	No data	HSDB 2008
Flashpoint	82.2 ºC	NIOSH 2006
Flammability limits	Practically nonflammable	HSDB 2008
Explosive limits	No data	HSDB 2008

HSDB = Hazardous Substances Data Bank; NIOSH = National Institute for Occupational Safety and Health;

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

5.1 PRODUCTION

Diazinon is the Ciba-Geigy Corporation trademark name for the active ingredient O,O-diethyl-O-(2-isopropyl-6-methyl-4-pyrimidinyl) phosphorothioate. This organophosphorus insecticide is produced commercially by reacting 2-isopropyl-4-hydroxy-6-methylpyrimidine and O,O-diethyl phosphorochloridothioate (HSDB 2008). It is also produced by condensation of isobutyramidine with acetoacetate to yield the intermediate, 2-isopropyl-4-methylpyrimidine, which is transformed to diazinon by treatment with diethylthiophosphate acid (Müller et al. 2005). Ciba-Geigy Corporation produced this chemical in McIntosh, Alabama until 1994 (SRI 1994, 1995). Currently, diazinon is produced by Drexel Chemical Company in Cordele, Georgia (SRI 2005).

In 1990, 4.67 million kg of diazinon were produced in the United States (Larkin and Tjeerdema 2000). No more recent production estimates for diazinon are available. As with many toxic chemicals, especially those whose production or use involves proprietary information, quantitative estimates of production are virtually impossible to obtain (Bason and Colborn 1992). As of June 30, 2001, manufacturing of indoor use products containing diazinon was discontinued. Manufacture of non-agricultural outdoor use products containing diazinon was discontinued as of June 30, 2003 (EPA 2004b). Production amounts of diazinon would be expected to decrease due to the discontinuation of all residential products containing this chemical.

Beginning on January 1, 1995, diazinon was listed as one of the newly added chemicals that manufacturing and processing facilities would be required to report under Title III of the Superfund Amendments and Reauthorization Act of 1986 (SARA) (Larkin and Tjeerdema 2000). Table 5-1 lists the production year, number of facilities, the state where each facility is located, and the range (in pounds) for each domestic manufacturer that reported the production or formulation of diazinon in 2005 (TRI05 2007). Manufacturers are required to report Toxics Release Inventory (TRI) data to satisfy EPA requirements. The TRI data should be used with caution since only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list.

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	6	100,000	9,999,999	1, 3, 4, 7, 9
AR	3	1,000	99,999	9, 12
CA	2	10,000	99,999	7
CO	2	10,000	999,999	7
FL	1	100,000	999,999	7
GA	7	1,000	9,999,999	2, 3, 4, 7, 9
IA	1	100,000	999,999	7
IL	1	1,000	9,999	12
KS	3	1,000	99,999	7, 8
LA	3	1,000	999,999	12
MO	5	1,000	9,999,999	7, 9
NE	1	10,000	99,999	12
NY	1	1,000	9,999	7
OH	7	100	9,999,999	7, 8, 12
TN	2	1,000	99,999	7, 12
TX	7	1,000	999,999	7, 9, 12
UT	1	10,000	99,999	12
WI	2	1,000	99,999	7
WY	1	10,000	99,999	7

[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

Source: TRI05 2007 (Data are from 2005)

5.2 IMPORT/EXPORT

Official government statistics on imports and exports for chemicals such as diazinon are summarized under broad generic categories such as "pesticides" or "organophosphates." In 1982, estimated diazinon imports to the United States were 6.41×10^4 kg (141,000 pounds) (HSDB 2008). No recent estimates are available on the volume of diazinon imported into the United States. Data on past and/or current import volumes are not adequate to assess trends in import volumes of this pesticide.

The U.S. EPA has no mandate to collect comprehensive data on pesticide exports, and does not have permission from the Department of Commerce to access the information in export declarations (Smith 2001). In a report by the Foundation for the Advancement of Science and Education, the authors report that no government agency maintains current records concerning what specific pesticides are exported by the United States. Between 1992 and 1994, 1.1 billion pounds of pesticides were exported with their exact chemical name omitted from the shipping records. Of the 25% of all pesticide exports that could be identified to a specific chemical, these authors identified export volumes of diazinon for 1992, 1993, and 1994 of 4.7 million, 5.0 million, and 3.4 million pounds, respectively. The remaining 75% of all exported pesticides could not be identified to a specific chemical (FASE 1996). According to U.S. Customs records, the United States exported an estimated 5.8 million pounds of diazinon from 1997 to 2000 (Smith 2001).

5.3 USE

Diazinon is an organophosphate pesticide that was first registered for use in the United States in 1956 (EPA 2004b). It was first developed as an insecticide, acaricide, and nematicide for use on a variety of pests for control of soil insects and pests of fruit, vegetables, and forage and field crops (EPA 2004b). Diazinon is used on ranges, pastures, grasslands, and ornamentals. It is used on grubs and nematodes in turf, in seed treatment, and in fly control (Meister et al. 2006). It is also used against flies in greenhouses and mushroom houses. Other uses include applications as a topically applied pesticide agent (e.g., aerosols, sprays, dips, ear tags) on non-lactating livestock to control biting insects or skin parasites (EPA 2004b; Wester et al. 1993; Worthing and Walker 1983).

With the steady elimination of older organochlorine pesticides from the market, diazinon has replaced many of the organochlorine pesticides such as chlordane. In addition to applications in agriculture, diazinon has been heavily used in urban areas (Banks et al. 2005). It had been used extensively in home and garden applications, in formulations designed to prevent such pests as crickets or cockroaches from

infesting homes or offices, and in pet collars (EPA 2004b). Residential application methods included aerosol cans, spray equipment, and granular spreaders. Due to the emerging health and ecological risks posed by diazinon, manufacturers agreed to phase out and cancel all residential products. As a result, after December 31, 2004, no diazinon products with residential uses would be registered or sold (EPA 2004b). It was also formerly used on golf courses and large sod farms for control of grubs and nematodes in turf, but these uses were suspended in the 1980s, first in the United States and then in Canada, after deaths occurred in migratory waterfowl (Frank et al. 1991a; Kendall et al. 1993). More cancellations and restrictions to be implemented in the future include: cancellation of all granular registrations (with some exceptions), deletion of aerial application for all uses (with some exceptions), deletion of foliar application on all vegetable crops, application rate reduction for ornamentals and lettuce, establishment of crop specific reentry intervals (REIs), cancellation of all seed treatment uses, engineering controls for all uses, reduction of the number of applications per growing season, and cancellation of use on some crops (EPA 2004b). Various types of diazinon formulations are produced including dusts, emulsifiable concentrates, granules, impregnated materials, microencapsulated forms, liquid, pressurized sprays, soluble concentrates, flowable concentrates, ready-to-use solutions, seed dressings, and wettable powders (EPA 2004b).

From 1987 through 1997, total annual domestic usage of diazinon was over 13 million pounds. However, most of this (about 70%) was allocated to outdoor residential uses (EPA 2004b). Since residential uses of diazinon have been discontinued, the total annual usage would be expected to be significantly lower. In the EPA Interim reregistration eligibility decision for diazinon (EPA 2004b), it was estimated that approximately 4 million pounds of active ingredient diazinon are used annually on agricultural sites. According to data from the Department of Pesticide Regulation's Pesticide Use Reports, the reported amount of diazinon used for both agricultural and reportable non-agricultural applications in California each year from 2000 to 2004 was 1,057,845; 1,001,294; 690,590; 523,786; and 492,050 pounds, respectively (California Environmental Protection Agency 2006).

5.4 DISPOSAL

Diazinon is currently considered a toxic chemical under Section 313 of the Emergency Planning and Community Right-To-Know Act (EPA 1995a, 1995b). Disposal of wastes containing diazinon is controlled by a number of federal regulations (see Chapter 8).

For ultimate disposal, large amounts of diazinon residuals should be incinerated in a unit with effluent gas scrubbing, while physical, chemical, and biological treatments may be appropriate for disposal of smaller quantities of diazinon. Two types of physical treatment systems, which have been tested and employed for pesticide wastes, are lined evaporation/degradation beds and granular activated sorption systems. Chemical treatment methods for pesticide waste degradation include photolysis, hydrolysis, and oxidation. Diazinon hydrolysis using sodium perborate and copper (+2) catalyst have been used (Felost et al. 2003).

Composting has been used for the disposal of diazinon-contaminated soils and organic solids. Diazinon was reported to undergo nearly complete degradation during composting of dairy manure. Complete degradation was also observed to occur within 4 weeks after application to turf and 6 weeks during composting of grass clippings (Felost et al. 2003).

Currently, empty pesticide containers should be triple rinsed with water and then transferred to a proper hazardous waste disposal facility. On February 11, 1994, the EPA proposed container design requirements for nonrefillable and refillable pesticide containers. This FIFRA authorized action also includes standards on pesticide removal from containers before disposal, standards for containment of bulk pesticide containers, and procedures for container refilling operations (26 FR 6712 "Standards for Pesticide Containers and Containment") (EPA 1994a).

No information was found on the past and present volumes of diazinon or diazinon-contaminated wastes disposed of by each disposal method.

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6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

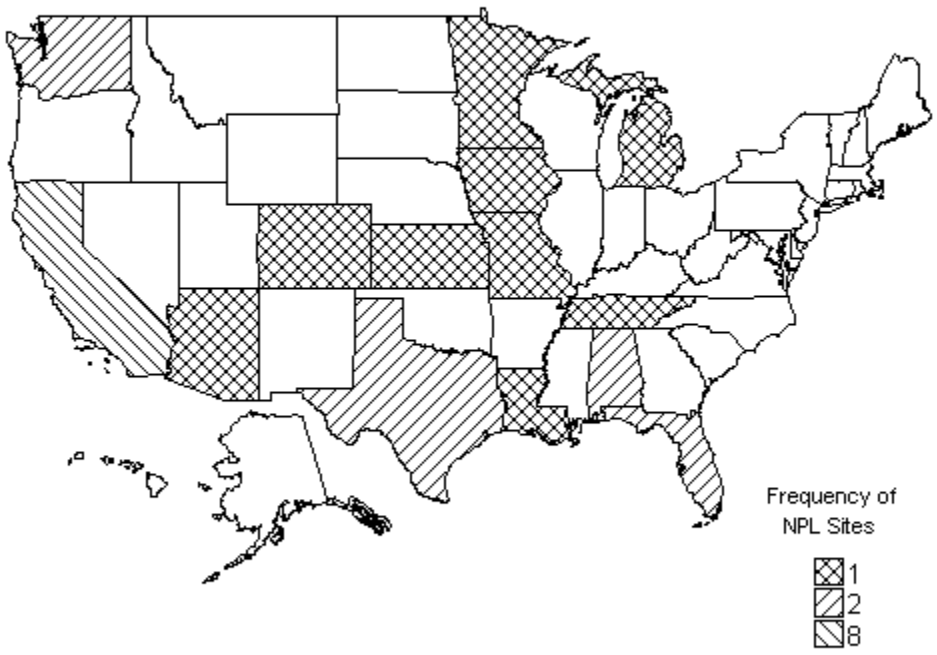
Diazinon has been identified in at least 25 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2008). However, the number of sites evaluated for diazinon is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, all are located within the United States.

Diazinon is released to the environment solely by human activities. Major atmospheric emissions result from volatilization of the chemical from soil resulting from its extensive use as an insecticide or from drift during pesticide application. Diazinon is released to surface waters directly by point source discharges, from drift during pesticide applications, and by runoff from agricultural and urban areas (EPA 1995a, 1995b).

Diazinon is found in all environmental compartments, but shows no pronounced tendency to partition to a particular environmental medium. Given adequate time, diazinon will be degraded by abiotic and biotic processes so that the parent compound is not persistent. Degradation products of diazinon include diazoxon, a toxic degradate, and 2-isopropyl-6-methyl-4-hydroxypyimidine (IMHP or oxypyrimidine), a persistent, less toxic degradate (EPA 2004b). Oxypyrimidine is the main soil and water degradate of diazinon (EPA 2004b). Diazinon has been detected in the atmosphere and trace amounts of its oxidation product (diazoxon) have also been detected. The diazoxon to diazinon ratio ranged from 0.056 to 7.1, but was generally <0.4 (Glotfelty et al. 1990a). In a study of diazinon use in the Central Valley of California, Seiber et al. (1993) reported that during daylight hours, the oxon to thion ratio in the atmosphere averaged 0.52, while at night, the ratio was 0.10. Diazinon can be converted to diazoxon in the atmosphere via ultraviolet (UV) radiation (Seiber et al. 1993). The estimated half-life for the vapor phase reaction of diazinon with hydroxyl radicals is approximately 4 hours (Meylan and Howard 1993). Diazinon can be transported moderate distances in the air from its original point of use (Zabik and Seiber 1993).

Diazinon released to surface waters or soil is subject to volatilization, photolysis, hydrolysis, and biodegradation. Biodegradation, primarily under aerobic conditions, is a major fate process for diazinon associated with water and soil. Diazinon can be biodegraded under anaerobic conditions as well. Hydrolysis is an important mechanism for degradation, particularly at low pH in water and soil. Diazinon has a relatively short half-life in water, ranging from 70 hours to 12 weeks depending on pH, temperature,

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



Derived from HazDat 2008

and sunlight as well as the presence of microorganisms (Chapman and Cole 1982; EPA 1976; Ferrando et al. 1992; Frank et al. 1991b; Scheunert et al. 1993; Schoen and Winterlin 1987; Sharom et al. 1980b). The half-life of diazinon in soil is influenced by the pH conditions in the soil and the soil type. The half-life values at pH 4, 7, and 10 were 66, 209, and 153 days, respectively, in sandy loam; 49, 124, and 90 days, respectively, in clay loam; and 14, 45, and 64 days, respectively, in sandy loam amended with peat (Schoen and Winterlin 1987). Diazinon is moderately mobile in some soils, particularly those with an organic matter content <3%, and can leach from soil into groundwater. If released to water, this pesticide does not bioaccumulate (bioconcentration factors [BCFs] values generally <100) in aquatic organisms.

In the United States, monitoring efforts under many national programs have not analyzed for this chemical. Diazinon has been identified in air samples from both rural and urban areas and in indoor air in both domestic and commercial buildings. It has also been detected in surface water, effluents from publicly owned treatment works (POTWs), and groundwater. It has been detected in soil and sediment in areas where it is extensively used in agriculture. Current information is lacking on the total amount of diazinon released to the environment and on the amount of diazinon that partitions into each environmental compartment.

The best-documented concern over diazinon relates to acute exposures of humans during or immediately following pesticide applications. This concern is warranted, since diazinon has been widely used, with many applications in urban areas (homes and gardens) that may have increased the possibilities of human exposure. In order to mitigate the exposure and risk to the general population, especially children, the EPA has phased out all residential uses of diazinon as of December 2004 (EPA 2004b). Diazinon and its major metabolite, diazoxon, have significant acute toxicity to humans. General population exposure to diazinon may occur through ingestion of contaminated food or drinking water and inhalation. Ingestion of foods contaminated with small residues of diazinon is the most likely route of exposure for the general population not living in areas where diazinon is extensively used. The general population may also be exposed to diazinon through inhalation of contaminated ambient (outdoor) air.

Populations living within or very near areas of heavy agricultural diazinon use would have an increased risk of exposure to relatively larger amounts of diazinon through dermal contact with contaminated plants, soils, surface waters, or artificial surfaces such as playground equipment and pavements; by inhalation of the mist formed from the applied insecticide; or by ingestion of water or food-borne residues. Those likely to receive the highest levels of exposure are those who are involved in the

production, formulation, handling, and application of diazinon, farm workers who enter treated fields prior to the passage of the appropriate restricted entry intervals, and workers involved in the disposal of diazinon or diazinon-containing wastes. Dermal contact appears to be the major route of exposure for workers. Inhalation of diazinon in occupational settings depends on its volatility, the type of formulation used, and the application technique employed.

6.2 RELEASES TO THE ENVIRONMENT

Diazinon has been released to the environment mainly as a result of its extensive use as an insecticide for household lawn and garden pest control, indoor residential crack and crevice treatments and pest collars, and agricultural pest control. In order to reduce exposure to children and others, a December 2000 agreement began a phase out of residential uses of diazinon, which was completed in December 2004. Future releases of diazinon will mainly be a result of agricultural use by aerial and ground spraying and spreading. For 1987 through 1997, total annual domestic usage of diazinon was over 13 million pounds. Approximately 4 million pounds of active ingredient diazinon are used annually on agricultural sites (EPA 2004b). There are no known natural sources of the compound. Diazinon has been identified in at least 25 of the 1,699 hazardous waste sites on the NPL (HazDat 2008).

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

6.2.1 Air

Estimated releases of 358 pounds (~0.16 metric tons) of diazinon to the atmosphere from 21 domestic manufacturing and processing facilities in 2005, accounted for about 1.5% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). These releases are summarized in Table 6-1.

Diazinon is released into the atmosphere solely by human activities associated with its production and use as an insecticide. These releases include releases to ambient air from production and from agricultural applications. Releases have also resulted from domestic lawn and garden applications, and releases to indoor air from pest-control treatment of domestic and commercial buildings. It appears that diazinon that has been applied to a field can undergo volatilization to the atmosphere (Glotfelty et al. 1990a; Schomburg et al. 1991; Seiber et al. 1993; Zabik and Seiber 1993). Glotfelty et al. (1990b) estimated that up to 24% of the diazinon applied to dormant peach orchards may be released through long-term volatilization losses even though volatilization quickly declines to low levels. Before residential use was cancelled in 2004 (EPA 2004b), home and garden application once accounted for over 40% of total diazinon usage; it is not possible to estimate volatilization from these applications.

Diazinon was detected in air at 1 of the 1,699 current or former NPL sites where diazinon has been identified in some environmental medium (HazDat 2008).

6.2.2 Water

Estimated releases of 10,287 pounds (~4.67 metric tons) of diazinon to surface water and to publicly owned treatment works (POTWs) from 21 domestic manufacturing and processing facilities in 2005, accounted for about 43% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). These releases are summarized in Table 6-1.

Diazinon is released into water directly from point source discharges, from drift during pesticide applications, and from nonpoint-source runoff from agricultural and urban areas. The use of permit compliance bioassay testing has helped identify point source discharges with acutely toxic effluents, and follow-up chemical analyses have pinpointed the identity of specific toxicants (Amato et al. 1992). Such work has led to the identification of diazinon as a cause of toxicity in POTW discharges (Amato et al. 1992; Burkhard and Jenson 1993). This is not surprising given the former widespread use of diazinon in

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

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	2	0	No data	0	0	0	0	0	0
AZ	1	0	No data	0	0	0	0	0	0
CA	1	0	No data	0	0	0	0	0	0
GA	2	9	5	0	0	0	14	0	14
KS	1	10	No data	0	0	0	10	0	10
LA	1	0	0	0	0	0	0	0	0
MO	1	0	No data	0	0	0	0	0	0
NE	1	0	No data	0	0	0	0	0	0
OH	2	250	0	0	0	0	250	0	250
TX	3	11	5,841	0	0	17	5,852	17	5,869
WY	1	250	No data	0	250	3	500	3	503
Total	16	530	5,846	0	250	20	6,626	20	6,646

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

RF = reporting facilities; UI = underground injection

Source: TRI05 2007 (Data are from 2005)

urban areas to control indoor pests and lawn and garden pests. It is easy for diazinon and its residues to reach the sewer collection systems for many POTWs.

In addition to loadings passing through sewage treatment systems, diazinon can reach surface waters directly from point source discharges (Braun and Frank 1980), from nonpoint-source inputs introduced from agricultural (Braun and Frank 1980; Kendall et al. 1993; Maguire and Tkacz 1993; Szeto et al. 1990; USGS 1993; Wan et al. 1994), or from suburban runoff (Frank et al. 1991b). It is impossible to obtain estimates of these loadings to surface waters. Water concentrations and transport of diazinon through the Sacramento-San Joaquin Delta and the adjacent portions of San Francisco Bay were studied in 1993 by the U.S. Geological Survey (USGS 1993). Diazinon was applied as a dormant spray in the Central Valley of California during 2 weeks of dry weather in January 1993. Pulses of elevated diazinon concentrations were detected in the Sacramento and San Joaquin Rivers after a series of rainstorms in early February 1993. All concentrations of diazinon measured in river and bay water samples exceeded 9 ng/L. Contaminated water samples collected from the San Joaquin River produced 100% mortality in bioassay tests conducted with Ceriodaphnia dubia for 12 consecutive days from February 8 to 19. The mortality of this sensitive indicator species was attributed to agricultural runoff of diazinon associated with the February rain events (USGS 1993). Banks et al. (2005) collected 1,243 surface water samples at 70 monitoring stations from rural and urban streams in Denton, Texas during the years of 2001–2004 and monitored for diazinon before and after the EPA ban on its residential uses. The total number of samples having diazinon concentrations above the lower limits of detection significantly decreased between 2001 and 2004, with the average diazinon concentration falling from 2.58 to 0.85 µg/L. These results indicate that the phasing out of residential uses of diazinon has led to a significant decrease in surface water occurrences (Banks et al. 2005).

Since diazinon is moderately mobile in soils under certain conditions, it has the potential to migrate through the soil and into groundwater. Detections have been made in some groundwater wells in the United States (Cohen 1986; EPA 1989). In areas with heavy applications of diazinon combined with irrigation or water-level adjustment techniques, diazinon detections in groundwater also have been documented (Cohen 1986; Frank et al. 1987, 1990b). It has not been possible to obtain quantifiable estimates of these diazinon loadings to groundwater.

Diazinon has been detected in surface water at 5 of the 1,699 current or former NPL sites and in groundwater at 8 of the 1,699 current or former NPL sites where diazinon has been identified in some environmental medium (HazDat 2008).

6.2.3 Soil

Estimated releases of 13,123 pounds (~5.95 metric tons) of diazinon to soils from 21 domestic manufacturing and processing facilities in 2005, accounted for about 55% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). No additional environmental releases via underground injection were reported (TRI05 2007). These releases are summarized in Table 6-1.

Diazinon is released into soils primarily from its registered use on various agricultural crops and its former use in home garden and lawn applications. Soils are the target for the vast majority of diazinon applications both as a nematocide and as an insecticide agent. In agricultural areas, diazinon may also be transferred to aquatic sediments (Domagalski and Kuivila 1993; Szeto et al. 1990; Wan et al. 1994). Since diazinon undergoes various activation and degradation reactions in the course of time ranging from hours to months, these loadings to soils and sediments are a temporary phenomena.

Diazinon has been detected in soil at 9 of the 1,699 current or former NPL sites and in sediment at 4 of the 1,699 current or former NPL sites where diazinon has been identified in some environmental medium (HazDat 2008).

6.3 ENVIRONMENTAL FATE

Diazinon can move into various environmental compartments, but there does not appear to be a major reservoir or sink for this chemical in any specific environmental compartment primarily because of its relatively rapid degradation in each environmental medium.

6.3.1 Transport and Partitioning

Based on its vapor pressure (see Table 4-2), if diazinon is released to the atmosphere, it will be expected to exist both in the vapor phase and particulate phase (Eisenreich et al. 1981). Glotfelty et al. (1990a) reported that during stagnant inversion fog events in the Central Valley of California, 56 and 19% of the diazinon in the air-phase was associated with vapor and aerosol particles, respectively, and only 24% of the diazinon was dissolved in the water phase. Schomburg et al. (1991) reported slightly different distributions for fog events resulting from advected oceanic fog. In this study, 26 and 10% of the diazinon in the air-phase was associated with vapor and aerosol particles, respectively; 62% of the

diazinon was dissolved in the water phase. Zabik and Seiber (1993) studied the atmospheric transport of diazinon from California's Central Valley to the Sierra Nevada Mountains. These samples collected during January through February 1991 represented the simultaneous collection of both vapor and particulate phases. Concentrations of diazinon and diazoxon were 13–10,000 and 4–3,000 pg/m^3, respectively, for samples collected at the 114 m elevation and 1.4–12 and 1.8–13 pg/m^3, respectively, at the 533 m elevation. The pesticide concentrations in air samples decreased with distance and elevation moving east from the Central Valley into the higher elevations of the Sierra Nevada Mountains. At times, air concentrations at the 114 m elevation were 1,000 times greater than concentrations detected at 533 m elevation. Concentrations at the 1,920 m elevation were typically below the limit of quantification. Wet deposition samples collected at the 114 m elevation contained up to 6,100 pg/mL diazinon and 2,300 pg/mL diazoxon.

Limited data based on atmospheric sampling and laboratory studies (Glotfelty et al. 1990a, 1990b) suggest a much greater potential for diazinon transport into the atmosphere after application to soils and vegetation. While the activation process (diazinon to diazoxon conversion) in the air would tend to transform diazinon fairly rapidly, the possibility of atmospheric transport means that this pesticide can move some distance from agricultural to nonagricultural areas (Glotfelty et al. 1990a, 1990b; Schomburg et al. 1991; Seiber et al. 1993; Zabik and Seiber 1993).

Diazinon released to water from both point and nonpoint sources may be emitted to the atmosphere by volatilization, sorbed to soils and sediments, or accumulated in aquatic organisms. While volatilization of diazinon may not be expected to be significant based upon the Henry's law constant (see Table 4-2), it can be an important transport process. Sanders and Seiber (1983) reported that 17% of the diazinon added to a model pond volatilized in 24 hours. Diazinon released to water also may be adsorbed moderately by soils and sediments based on its organic carbon partition coefficient (K_{oc}) values measured in soil (Sharom et al. 1980a). Because this pesticide is only moderately adsorbed by some soils, leaching into groundwater can occur.

Diazinon does not significantly bioaccumulate in aquatic organisms. A comparison of BCF values obtained for various freshwater and saltwater fish and invertebrate species is presented in Table 6-2. The BCF values generally range from 4 to 337, but there are only a few cases where the measured BCF value for diazinon exceeds 100. In those experiments where testing was continued for several days after exposure to the diazinon had ended, tissue residues generally decreased rapidly within 1–5 days (El Arab et al. 1990; Sancho et al. 1993; Tsuda et al. 1989, 1990, 1995). Despite the fairly low BCF values, some

Table 6-2. Bioconcentration Data for Diazinon

Species common name/ Scientific name	Exposure type	Duration (days)	BCF[a]	Reference
Freshwater				
Shrimp/*Paratya compressa compressa*	F	3	4	Seguchi and Asaka 1981
Oriental weatherfish/*Misgurnus anguilli candatus*	F	14	28	Seguchi and Asaka 1981
Common carp/*Cyprinus carpio*	F	3	130	Seguchi and Asaka 1981
Perch/*Sarotherodon galilaeus*	S	3	39	El Arab et al. 1990
Rainbow trout/*Oncorhynchus mykiss*	F	3	92	Seguchi and Asaka 1981
Brook trout/*Salvelinus fontinalis*	F	210	25	EPA 1977
Guppy/*Poecilia reticulata*	R	2	39	Keizer et al. 1991
Zebra fish/*Brachydanio rerio*	R	2	300	Keizer et al. 1991
Willow Shiner/*Gnathopogon caerulescens*	F	7	248	Tsuda et al. 1989
Killifish/*Oryzias latipes*	F	3	20	Tsuda et al. 1995
Killifish/*O. latipes*	F	7	94	Tsuda et al. 1997
Fathead minnow/*Pimephales promelas*	F	2B304	337[b]	Veith and Kosian 1983
Goldfish/*Carassius aurapus*	F	7	49	Tsuda et al. 1997
White cloud mountain fish/*Tanichthys albonubes*	F	7	36	Tsuda et al. 1997
Saltwater				
Sheepshead minnow/*Cyprinodon variegatus*	F	108	147	Goodman et al. 1979

[a]BCF listed is the highest BCF value reported in the cited reference.
[b]Calculated quantitative structure-activity relationship (QSAR) value as reported in ASTER.

BCF = bioconcentration factor; F = flow-through exposure system; S = static system; R = renewal system

researchers still recommend caution in consuming some aquatic species (EPA 1993c; Keizer et al. 1991). This is in large measure because the mechanisms that fish and invertebrates use to metabolize diazinon are poorly understood and seem to vary widely from species to species. In addition, diazinon and its metabolites have not been widely monitored in aquatic species. Since some of the metabolites of diazinon are themselves toxic, a measure of caution may still be in order in cases where there is reason to believe edible fish or shellfish have had recent exposure to diazinon (Keizer et al. 1991). This is partially the basis for the EPA recommendation to states to consider routine monitoring for diazinon in edible fish and shellfish species as part of their state toxics monitoring programs particularly in those watersheds where extensive use of diazinon is identified (EPA 1993c).

Diazinon released in soil from its registered uses partitions to the atmosphere through volatilization, to surface water via runoff, and to groundwater as a result of leaching. According to Kenaga (1980), chemical compounds with a K_{oc} of <100 are considered moderately to highly mobile; diazinon with a K_{oc} value of 40–432 (mean of 191), therefore, would be considered moderately mobile. Additional parameters influencing the leaching potential of this chemical include the soil type (e.g., clay versus sand), the amount of rainfall, the depth of the groundwater, and the extent of degradation. In laboratory tests of sand and organic soil, Sharom et al. (1980a) found that 26, 22, 11, 11, and 7% of the diazinon leached from sand (after five successive 200 mL rinses), respectively. A total of 95% of the diazinon added to the sand leached after 10 successive 200 mL rinses. In organic soil, however, only 3, 4, 11, 9, and 7% of the diazinon leached from soil (after five successive 200 mL rinses), respectively. Only 50% of diazinon added to the organic soil leached after 10 successive 200 mL rinses. While diazinon can show sorption in soils with high organic content (>3%), in most other soil types, diazinon has properties suggesting a moderate potential for leaching into groundwater (Arienzo et al. 1994; Sharom et al. 1980a). Arienzo et al. (1994) tested the adsorption and mobility of diazinon in 25 soils with different physicochemical properties. Diazinon was found to be slightly mobile in 80% of the soils tested (those with organic matter content <3%), and immobile in 20% of the soils tested (those with organic matter content >3%). The compound leached primarily from light soils with low organic matter content. Levanon et al. (1994) assessed the impact of plow tillage on microbial activity and the fate of diazinon and other pesticides in the top 5 cm soil layer. A higher leaching rate for diazinon was detected in plow tillage soils than in no-tillage soils after incubation for 21 days. The no-tillage soils were characterized by a higher organic matter content and higher microbial populations and activity than the plow tillage soils.

Arienzo et al. (1993) conducted a study of adsorption and mobility of diazinon in soils from aqueous media and mixtures of methanol-water and hexane-water. Adsorption of diazinon by soils from aqueous

systems was related to organic matter content (i.e., the higher the organic content, the greater the adsorption). In methanol-water and hexane-water systems, the adsorption of diazinon by soils decreased. This situation may arise at hazardous waste disposal sites where pesticide waste residues and cosolvents may be encountered together. The presence of these organic solvents will increase the mobility (leachability) of diazinon in the soil and increase the potential for groundwater contamination. Diazinon has been detected in groundwater in the United States (Cohen 1986; EPA 1989; HazDat 2008), and in the Great Lakes region of Ontario, Canada (Frank et al. 1987, 1990b).

6.3.2 Transformation and Degradation

Diazinon is subject to a variety of abiotic and biotic degradation processes in all environmental compartments.

6.3.2.1 Air

Diazinon, once released to the atmosphere, may be subject to direct photolysis since it absorbs light in the spectra above 290 nm (Gore et al. 1971). Glotfelty et al. (1990a), Schomburg et al. (1991), Seiber et al. (1993), and Zabik and Seiber (1993), all reported the presence of diazinon and its activated product (diazoxon) in atmospheric samples. Glotfelty et al. (1990a) believe that diazoxon is formed by atmospheric oxidation especially during the daylight hours. Schomburg et al. (1991) reported that diazinon undergoes transformation to diazoxon during atmospheric transport from agricultural to non-agricultural areas. Seiber et al. (1993) reported mean concentrations of diazinon of 76.8 ng/m^3 and of diazoxon of 10.8 ng/m^3 in air samples collected near fruit and nut orchards in Parlier, California. The half-life (first-order kinetics) for the vapor phase reaction of diazinon with hydroxyl radicals in the atmosphere is estimated to be 4 hours, assuming an atmosphere containing $5x10^5$ hydroxyl radicals/m^3 at 25 EC (Meylan and Howard 1993).

6.3.2.2 Water

Diazinon released to water may be subject to both abiotic degradation (i.e., hydrolysis and photolysis) and biotic degradation by microorganisms. The rate of abiotic degradation is influenced strongly by pH and temperature. In a laboratory study, Chapman and Cole (1982) reported that pH alone influenced the half-life of diazinon maintained in sterile water-ethanol (99:1) phosphate buffer solutions at 25 EC. Degradation of diazinon was most rapid under acidic conditions with half-life values in weeks (days shown in parentheses) (first-order kinetics) of 0.45 (3.15), 2.0 (14), 7.8 (54.6), 10.0 (70), and 7.7 (53.9) at

pH values of 4.5, 5.0, 6.0, 7.0, and 8.0, respectively. Garcia-Repetto et al. (1994) also studied the influence of pH on the degradation of diazinon in water-ethanol (9:1) solutions maintained between 15 and 31 EC. These authors reported estimated half-life values (first-order kinetics) for diazinon of 1.31, 8.57, and 8.19 days at pH values of 2, 7.5, and 8.7, respectively. The higher temperatures and lower pH conditions of this study may account for the more rapid degradation rates. Frank et al. (1991b) followed the degradation of diazinon in natural surface/groundwater samples at pH 8.2 that were either stored in the laboratory at 4 EC in the dark or at 21 EC under ambient indoor fluorescent light conditions for 125 days. Under the two temperature and light regimes the half-life values (first-order kinetics) of diazinon were 14 days (light at 21 EC) and 45 days (dark at 4 EC). Degradation was more affected by temperature, suggesting that hydrolysis was the primary mode of degradation (Frank et al. 1991b).

EPA (1976) reported that diazinon absorbs sunlight less than some of its organophosphate relatives, but that diazinon undergoes direct photolysis in water. The estimated half-life (first-order kinetics) for photolysis in aqueous solutions maintained in glass cells and irradiated with a mercury vapor lamp (>290 nm) was 1,000 hours (42 days). Frank et al. (1991b) investigated the degradation of diazinon in surface water and groundwater samples, but found little difference in the rate of diazinon degradation in light and dark conditions. The half-life (first-order kinetics) of diazinon of 88 days (light) and 99 days (dark) suggests that photolysis was not a major factor in degradation.

Scheunert et al. (1993) studied the effects of photodegradation (via exposure to sunlight) on diazinon dissolved in distilled water, in a humic acid aqueous solution, and in natural water samples from the Isar and Rhine Rivers and Lake Ammersee in Germany with comparable samples maintained in the dark at 25 EC. In the dark, river water had a higher diazinon degradation capacity than distilled water. The degradation capacity of natural water samples was further enhanced by exposure to sunlight. The highest degradation capacity was observed for the Rhine River water which also had the highest oxygen and hydroxyl ion concentration and the highest pH value (8.1) of the natural waters tested.

Mansour et al. (1997) studied the photodegradation of diazinon under UV irradiation in a water/soil suspension and found that diazinon was converted, among other products, to the isomeric isodiazinon. Photodegradation was increased in the presence of titanium dioxide, hydrogen peroxide or ozone, or by using natural-river or lake water.

Sharom et al. (1980b) studied the degradation of diazinon under laboratory conditions using both distilled water and natural water samples. Degradation was more rapid in natural water (pH 7.7) (12 weeks) than

in sterilized natural water, sterilized distilled water, or distilled water (>16 weeks), suggesting that biodegradation of diazinon was occurring. Ferrando et al. (1992) conducted a laboratory microcosm study using both natural surface water and tap water. These experiments were conducted in aerated aquaria, maintained at 22 EC with a 12-hour light:dark period. The pH of the natural water was 9.0 and that of the tap water was 7.5. The half-life values (first-order kinetics) of 71 and 79 hours for the natural and tap water samples, respectively, both indicate rapid degradation. Under these experimental microcosm conditions, hydrolysis, photolysis, and biodegradation may all be operative in the natural water system. Wide discrepancies in the rates of diazinon degradation in water reported in the literature appear to be influenced by both abiotic and biotic factors.

Bondarenko et al. (2004) investigated the persistence of diazinon in natural waters from different locations within the Upper Newport Bay-San Diego Creek watershed located in central Orange County, California. First-order half-lives for diazinon were 6.3–14.0 and 25.0–28.3 days in natural water at 21 and 10 °C, respectively, and 51.1–54.9 days in sterilized water at 21 °C. The first-order half-lives for diazinon in seawater were 41.0 and 124.0 days at 21 and 10 °C, respectively. The results of the study suggest that under similar pH conditions, the persistence of diazinon may be prolonged in seawater. Sterilization greatly increased persistence of diazinon in freshwater, indicating that degradation in freshwater was largely attributed to microbial activity. Diazinon was found to be degraded primarily by abiotic processes in seawater, and the lack of microbial degradation likely contributed to its prolonged persistence in the seawater. Degradation in freshwater also showed temperature dependence, with significantly faster dissipation of diazinon at 21 °C when compared to 10 °C (Bondarenko et al. 2004).

Although diazinon has been detected in groundwater samples in both the United States and Canada (Cohen 1986; EPA 1989; Frank et al. 1987, 1990b; HazDat 2008), no studies were identified concerning diazinon transformation and degradation processes within aquifers. Based on theoretical considerations, abiotic hydrolysis mechanisms would be expected to degrade diazinon within a few months (Chapman and Cole 1982; Cowart et al. 1971).

6.3.2.3 Sediment and Soil

Once released to soils and sediments, diazinon can be degraded by hydrolysis, photolysis, and biodegradation by several genera of microorganisms. Microbial degradation appears to be the major pathway for the degradation of diazinon in soils; however, under anaerobic conditions, abiotic hydrolysis

appears to be the most probable mechanism responsible for degradation of the compound under acidic soil conditions (Larkin and Tjeerdema 2000).

The influence of soil pH on the persistence of diazinon was studied by Chapman and Cole (1982). Diazinon degradation was found to be more rapid in organic soils with pH values of 6.1 and 5.2 than in mineral soils with pH values of 6.8 and 8.0, and was slightly more rapid in the more acidic organic soil. Schoen and Winterlin (1987) conducted an extensive study of the effects of various soil factors and organic amendments on degradation of diazinon. The factors affecting the rate of diazinon degradation in soil were pH, soil type, organic amendments, soil moisture, and pesticide concentration. Soil pH was a major factor affecting degradation. At a soil concentration of 100 ppm diazinon and 50% water saturation, estimated half-life values (first-order kinetics) at pH 4, 7, and 10 were 66, 209, and 153 days, respectively, in sandy loam; 49, 124, and 90 days, respectively, in clay loam; and 14, 45, and 64 days, respectively, in sandy loam amended with peat. Loss of diazinon occurred in the order of sandy loam with peat > clay loam > sandy loam. Addition of acidic peat to the soil lowered the pH and could have been responsible for increased hydrolysis. Degradation of diazinon in soil was most favorable when the pesticide was present at low concentrations in moist soil, amended with peat or acidified to a pH of 4, and least favorable at high diazinon concentrations in neutral or basic mineral soil (Schoen and Winterlin 1987). It has been observed that dissipation of diazinon from soil slows significantly as concentration increases above a certain level, possibly due to microbial toxicity which inhibits degradation (Felost et al. 2003). Prolonged persistence of diazinon in soil increases the potential for runoff and leaching.

In six types of soils, Somasundaram et al. (1991) reported that diazinon was hydrolyzed to 2-isopropyl-6-methyl-4-hydroxypyrimidine (IMHP) and that the degradation product was significantly more mobile in these soils than its parent compound diazinon. In an earlier study, Somasundaram et al. (1989) found that prior applications of IMHP did not enhance degradation of diazinon.

In a study of degradation of diazinon in three submerged tropical soils, only 2–6% of the originally applied diazinon remained 50–70 days post-application (Sethunathan and MacRae 1969). Degradation of diazinon was more rapid in nonsterilized soils, indicating microbial participation in two of the three soil types. In the third type (an acid clay soil), diazinon degradation was more rapid in the sterilized samples at pH 4.7, apparently because of the compound's instability under acid conditions. Streptomyces sp. isolated from the submerged soils could degrade the diazinon. In a field study of a treated cranberry bog by Szeto et al. (1990), disappearance of diazinon from irrigation ditch sediment (pH 4.4) and from sediment in an adjacent reservoir (pH 5.0) was equally rapid. These authors found that <1% of diazinon

remained 38 and 22 days post-application in the irrigation ditch and reservoir sediments, respectively. In nonsterilized soil, diazinon degradation was faster at 100% water saturation than at 50% water saturation. These results suggest that microbial activity under anaerobic conditions plays an important role in diazinon degradation (Schoen and Winterlin 1987).

Photolysis of diazinon on soil surfaces was studied by Burkhard and Guth (1979). The effectiveness of photolysis in 24 hours was only slightly greater on moist soil surfaces (51%) than it was on dry soil surfaces (44%) at 45 EC. The major photolytic product identified for diazinon was 2-isopropyl-6-methyl-4-hydroxypyrimidine. This same reaction product was found for acid hydrolysis and photolysis in aqueous solutions or on soil.

Photochemical reactions in soil are significant only at the surface. When the surface soil is moist, photolysis may occur both with the portion dissolved in water and with the portion adsorbed to the soil. Mansour et al. (1997) studied the photochemical reaction of diazinon in water/soil suspensions in order to include the possible catalytic effects of adsorption. Under UV irradiation in a water/soil suspension, diazinon was converted to, among other products, the isomeric isodiazinon. Photodegradation was increased in the presence of titanium dioxide, hydrogen peroxide, or ozone, or by using natural river water or lake water.

Gunner and Zuckerman (1968) reported synergistic microbial degradation of diazinon by two microorganisms, Arthrobacter sp. and Streptomyces sp. When Arthrobacter sp. and Streptomyces sp. were incubated separately on growth media where diazinon was the primary carbon source, neither was able to convert the pyrimidinyl carbon to carbon dioxide. When incubated together, only 6% of the parent diazinon remained, and 94% was converted to two unidentified metabolites. Two microorganisms isolated from flood soils also were found to hydrolyze diazinon (Adhya et al. 1981). Diazinon was rapidly hydrolyzed within 24 hours by both Flavobacterium sp. and Pseudomonas sp. A hydrolysis product of diazinon, IMHP, was metabolized more rapidly by the Flavobacterium sp. than the Pseudomonas sp. More recently, oxypyrimidine was reported to be the major soil degradation product of diazinon and is considered to be more persistent than diazinon (Larkin and Tjeerdema 2000). Barik and Munnecke (1982) reported that an enzyme (parathion hydrolase) obtained from Pseudomonas sp. cultures could hydrolyze diazinon in soils. More than 98% of 10,000 ppm of diazinon in soil can be degraded within 24 hours if sufficient buffer and enzyme are added to the contaminated soil. The authors report that it is technically feasible to use parathion hydrolase to clean up diazinon spills in the environment.

Levanon et al. (1994) studied the effects of plow tillage on microbial activity and the degradation of diazinon in the 0–5 cm soil layer. In no-tillage soils, higher microbial populations and activity were associated with higher mineralization rates of diazinon (45% mineralization after 76 days). Enhanced transformation rates played a role in minimizing leaching from no-tillage soils. Synergistic effects between fungi and bacteria in the degradation of diazinon were also observed. The authors noted that almost no mineralization of the compound occurred when either fungi or bacteria were selectively inhibited, demonstrating synergism between the two microbial communities. A higher proportion of diazinon leached from the plow tillage soils than from the no-tillage soils. Microbial population and activity measured as biomass, bacterial counts, hyphal length of fungi, and carbon dioxide evolution were all higher in samples of no-tillage soils.

6.3.2.4 Other Media

Michel et al. (1997) studied the fate of diazinon during the composting of leaves and grass. The yard trimmings were amended with ^{14}C labeled diazinon and composted for 54 days. During composting, 11% of the ^{14}C-diazinon was mineralized to carbon dioxide. A water extract of the finished compost contained 36% of the added ^{14}C and analysis of this extract indicated that the ^{14}C was in the form of 2-isopropyl-IMHP, a hydrolysis product of diazinon. The remaining fraction of ^{14}C was unidentifiable or associated with a high molecular weight extract fraction. The results show that during the composting, a relatively small amount of diazinon is mineralized to carbon dioxide, while a majority is hydrolyzed to potentially leachable but less toxic IMHP, high molecular weight residues, and unextractable residues that are presumed to have low bioavailability.

Diazinon has been detected at a variety of waste water treatment plants. Zhang and Pehkonen (1999) investigated the oxidation of diazinon by aqueous chlorine and reported that the half-life is only several minutes at typical chlorine concentrations found in waste water treatment plants. The oxidation product of diazinon was reported to be diazoxon.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to diazinon depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of diazinon in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on diazinon levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily

equivalent to the amount that is bioavailable. The analytical methods available for monitoring diazinon in a variety of environmental media are detailed in Chapter 7.

Most information on diazinon concentrations in various environmental media derived from large scale monitoring networks dates from before the mid-1980s and no longer reflects current conditions. There is a noticeable lack of national monitoring studies that would allow meaningful estimation of current diazinon concentrations associated with various environmental media. Reliable evaluation of the potential for human exposure to diazinon depends in part on the reliability of supporting analytical data from environmental samples and biological specimens.

6.4.1 Air

Diazinon concentrations in the atmosphere were monitored in several national studies during the 1970s and 1980s and more recently in several regional studies. Diazinon has been measured in outdoor air samples in both rural and urban environments, near production facilities, and in indoor air (associated with its use for pest control in domestic and commercial buildings).

In a study of pesticide residues in ambient air sampled in 14–16 states during 1970, 1971, and 1972, diazinon was detected in 50% of the 2,479 samples analyzed, with a mean concentration of 2.5 ng/m^3 and a maximum concentration of 62.2 ng/m^3 (Kutz et al. 1976). Carey and Kutz (1985) reported that ambient air concentrations of diazinon collected from February through September 1980 in Perkin, Illinois, ranged from 1.3 to 10 ng/m^3.

In a study of pesticide levels in ambient suburban air, diazinon was detected in 80, 80, and 40% of samples collected in three cities (Miami, Florida; Jackson, Mississippi; and Fort Collins, Colorado), respectively. The maximum diazinon concentration detected in each city was 3.9, 2.0, and 2.2 ng/m^3 for Miami, Florida; Jackson, Mississippi; and Fort Collins, Colorado, respectively (Kutz et al. 1976). During 1973–1974, diazinon concentrations in air were measured in urban Miami, Florida, and in the adjacent Everglades National Park. Urban diazinon levels ranged from not detectable to 3.3 ng/m^3 (1.5 ng/m^3 mean); corresponding levels in Everglades National Park ranged from not detectable to 1.9 ng/m^3 (0.6 ng/m^3 mean) (Lewis and Lee 1976). Nationwide, diazinon was detected in 48% of 123 urban air samples collected in 10 U.S. cities during 1980. The maximum diazinon concentration reported was 23 ng/m^3 (mean 2.1 ng/m^3) (Carey and Kutz 1985).

Most recently, non-occupational exposure to diazinon among residents of two U.S. cities (Jacksonville, Florida, and Springfield, Massachusetts) was studied over three seasons: summer 1986, spring 1987, and winter 1988 (Whitmore et al. 1994). The study focused primarily on inhalation exposures with primary environmental monitoring consisting of 24-hour indoor and outdoor air. For the Jacksonville, Florida, population, the estimated mean diazinon concentrations were 85.7–420.7 ng/m^3 in indoor air and 1.1–13.8 ng/m^3 in outdoor air. For the Springfield, Massachusetts, population, mean exposures were much less. The estimated diazinon concentrations were 2.5–48.4 ng/m^3 in indoor air and 8.2–9.2 ng/m^3 in outdoor air.

Ambient diazinon concentrations were measured under foggy atmospheric conditions in and around the Central Valley of California (Parlier, California), which is a prime agricultural area dominated by fruit, nut, and citrus orchards (Glotfelty et al. 1990a; Seiber et al. 1993; Zabik and Seiber 1993). In fog, diazinon concentration was 1.6 ng/m^3 and diazoxon (the oxon transformation product) concentration was 0.82 ng/m^3. In a similar study, Schomburg et al. (1991) analyzed air and fog near Monterey, California, to determine whether the uptake of diazinon in advected oceanic fog was different from uptake in fog collected under stagnant inversion conditions in the Central Valley of California. Fog water concentrations of diazinon ranged from 0.15 to 4.8 µg/L in coastal areas; higher concentrations ranging from 0.31 to 18 µg/L were found in the Central Valley area. Diazinon and diazoxon favored the aqueous phase in foggy atmosphere, with 62.4 and 87.8%, respectively, reported in the aqueous phase. Zabik and Seiber (1993) studied the atmospheric transport of diazinon from California's Central Valley to the Sierra Nevada Mountains. Air samples collected from January through February 1991 represented the simultaneous collection of both vapor and particulate phases. Concentrations of diazinon and its oxon were 13–10,000 pg/m^3 (0.013–10 ng/m^3) and 4–3,000 pg/m^3 (0.004–3 ng/m^3), respectively, for samples collected at the 114 m elevation and 1.4–12 pg/m^3 (0.0014–0.012 ng/m^3) and 1.8–13 pg/m^3 (0.0018–0.013 ng/m^3), respectively, at the 533 m elevation. The pesticide concentrations in air samples decreased with distance and elevation moving east from the Central Valley into the higher elevations of the Sierra Nevada Mountains. At times, air concentrations of diazinon at the 114 m elevation were 1,000 times greater than concentrations detected at 533 m elevation. Concentrations at the 1,920 m elevation were typically below the limit of quantification. Wet deposition samples (rain and snow) collected at the 114 m elevation contained up to 6,100 pg/mL diazinon and 2,300 pg/mL diazoxon. Diazinon was detected in 100% of air samples collected from over the Mississippi River from New Orleans, Louisiana, to St. Paul, Minnesota, during the first 10 days of June 1994 at a mean concentration of 0.08 ng/m^3 (Majewski et al. 1998). The maximum concentration detected, 0.36 ng/m^3, was detected near a major metropolitan area.

Diazinon residues in ambient air sampled within 800 m of two pesticide formulation plants in Arkansas (from 1970 to 1972) and within 275 m of a pesticide formulation plant in Tennessee (in 1971) were 0.3–18.0 ng/m^3 (mean 2.2 ng/m^3) and 0.5–27.9 ng/m^3 (mean 7.3 ng/m^3), respectively (Lewis and Lee 1976).

In addition to its presence in the ambient atmosphere, diazinon also has been monitored in both outdoor and indoor air associated with its use in a variety of domestic, commercial, and occupational exposure situations. Exposure to diazinon from its use in lawn and home garden applications was evaluated by Davis et al. (1983). Diazinon was mixed with water and sprayed using compressed air sprayers or hose-end sprayers, and potential respiratory and dermal exposures were estimated from residues collected from respirator filters, body pads, and hand rinsings. These authors reported mean respiratory exposures of 1.9, 2.9, and 7.4 μg/hour associated with use of compressed air sprayers on lawns, compressed air sprayers on shrubs, and hose-end sprayers on lawns, respectively. The amount of diazinon collected in the respiratory pads was negligible compared to the amount collected on dermal pads. Total dermal exposures were 5,700, 7,500, and 29,000 μg/hour, respectively, for the three sprayer types; however, dermal exposure of the hands alone accounted for ≥85% of the total dermal exposure for each sprayer type.

Diazinon air concentrations related to vapors released from pest control strips were measured by Jackson and Lewis (1981). Diazinon levels in indoor air increased from 0.32 μg/m^3 at 6 hours after application of the pest strips to 1.34 μg/m^3 on day 15, and then declined to 1.21 μg/m^3 on day 30. Air sampling in a retail garden store where pesticide containers with diazinon were displayed showed an average diazinon concentration of 3.4 μg/m^3 (Wachs et al. 1983).

Currie et al. (1990) evaluated the concentrations of diazinon in indoor air and on working surfaces for a period of 10 days after application in commercial offices. The highest concentrations of diazinon (163 and 158 μg/m^3) were measured 4 hours post-application in two empty offices, while the concentration in the furnished office was 27 μg/m^3. One day post-application, levels were 125 and 70 μg/m^3 in the two empty offices, and 27 μg/m^3 in the furnished office. Air concentrations of diazinon continued to decline and on day 6 post-application were approximately 35 μg/m^3 in the empty offices and 8 μg/m^3 in the furnished office. Airborne levels of diazinon were distinctly lower in the furnished office, and this was attributed to obstruction of the applicator's spraying path by office furniture so that a lower amount of diazinon was applied. Diazinon deposition on aluminum plates was measured as an indicator of surface contamination, measurements ranged from 0.4–15 ng/cm^2. No overall decrease in surface contamination occurred over time. Plates suspended 1.5–2.1 m above the floor generally exhibited higher

diazinon levels 24 hours post-treatment than at 1–2 hours post-treatment. The authors believe that this was a result of evaporation of diazinon from the carpeted floor augmented by air turbulence. Diazinon contamination measured by surface wipes on furniture and foil on carpet ranged from 13 to 38 ng/cm^2.

Diazinon levels in indoor air were monitored in an animal facility treated monthly with a 1% aqueous diazinon formulation (Williams et al. 1987). Indoor air sampling was conducted in two areas frequented regularly by facility personnel, the lounge and cage-washing areas. The lounge areas were enclosed rooms while the cage-washing areas were open-ended and were in effect part of the corridor system of the facility. Air samples were collected using adsorbent sampling tubes (Supelco-20 P) for 4 hours at 1.8 L/minute just prior to spraying on days 0, 28, and 56, approximately 16–20 hours post treatment, and at various intervals thereafter. Diazinon levels increased immediately after spraying, but decreased rapidly to 2–3 μg/m^3 in <1 day and continued to decrease to <0.05 μg/m^3 until the next spraying. During many months of diazinon application there was little buildup in background diazinon air levels (<0.5 μg/m^3).

Lenhart and Kawamoto (1994) reported air concentrations of up to 297 μg/m^3 in greenhouse air after spray applications of an emulsifiable concentrate of diazinon, under the trade name Clean Crop AG500, and concentrations up to 3,030 μg/m^3 in greenhouse air after a 4-hour cold fogging application of the same formulation.

Palmgren and Lee (1984) collected samples of grain dust (dust accumulated in the dust collection systems of grain elevators) from six grain elevators located in the New Orleans, Louisiana, area to evaluate potential occupational exposures of grain elevator personnel. Diazinon concentrations in grain dust were <0.01 μg/g for all 31 samples collected.

6.4.2 Water

Carey and Kutz (1985) reported that the maximum diazinon residue collected in a national surface water monitoring program conducted from 1976 to 1980 was 2.38 μg/L and that diazinon was detected in only 1.2% of the samples collected. Pereira and Hostettler (1993) conducted a study of the Mississippi River and its tributaries during 1991 and 1992. These authors reported that diazinon was detected in water samples from the Illinois River at concentrations of 20 ng/L and from several sites on the mainstem of the lower Mississippi River at concentrations ranging from 4 to 10 ng/L. During 1991, Domagalski and Kuivila (1993) monitored diazinon concentrations in water and suspended sediment collected at various

sites in San Francisco Bay during low river discharge and after spring rain events. Diazinon was detected in water only after the spring rains and most (98%) of the diazinon was in the dissolved phase. Concentrations dissolved in the water column ranged from 4.6 to 14.6 ng/L. The authors suggest that diazinon may be close to equilibrium with respect to sorption or desorption on suspended sediment particles.

In the Great Lakes region, diazinon was detected in surface waters in several river basins in southern Ontario, Canada. Braun and Frank (1980) monitored surface water concentrations of 8 organochlorine and 12 organophosphate pesticides in 11 agricultural watersheds in southern Ontario. All watersheds drained into the Great Lakes. Diazinon residues as a result of field use were detected in only one water shed, but the chemical was repeatedly detected in 34% of samples (1975–1976) and 74% of samples (1976–1977) collected from one creek. The source of the diazinon was traced to its indoor use to control flies in a series of mushroom houses that discharged via a drainage tile system directly to the creek. The maximum residues of diazinon in the stream were 140 µg/L (5.75 µg/L mean) and 26 µg/L (1.02 µg/L mean) in 1975–1976 and 1976–1977, respectively. Frank and Logan (1988) measured pesticide and industrial chemical residues at the mouth of the Grand, Saugeen, and Thames Rivers in southern Ontario, Canada, from 1981 through 1985. River water samples collected at the mouths of the three rivers (that drain into the Great Lakes) were analyzed for 20 herbicides, 3 fungicides, and 25 insecticides including diazinon. One water sample collected during May through August 1982 contained a mean diazinon concentration of 0.21 µg/L. Maguire and Tkacz (1993) monitored concentration of pesticides in surface water near the mouths of the Yamaska River in Quebec, Canada, and five of its tributaries during 1986 and 1987. Diazinon was detected at the mouth of the Yamaska River at concentrations ranging from 2.1 to 11.9 ng/L, at the mouth of the Saint-Nazaraire River at concentrations ranging from 3.1 to 26.7 ng/L, and at the mouth of the Salvail River at concentrations ranging from 1.1 to 4.9 ng/L. Frank et al. (1990a) conducted a survey of 211 rural ponds in southern Ontario and measured concentrations of 29 herbicides, fungicides, and insecticides including diazinon. Two ponds were found to be contaminated with diazinon, and residues in pond water ranged from 0.6 to 1.7 µg/L (1.2 µg/L mean). The source of the diazinon in these two cases was attributed to accidental pesticide spills during agricultural application. In the U.S. Geological Survey's National Water-Quality Assessment Program 1999–2000, surface water samples from the Yakima River Basin, Washington were collected at 34 sites and analyzed for the occurrence of pesticides (USGS 2002a). Diazinon was detected in 16 of 98 surface water samples at concentrations ranging from <0.002 to 0.169 µg/L. Banks et al. (2005) collected 1,243 surface water samples at 70 monitoring stations from rural and urban streams in Denton, Texas during the years of 2001–2004 and monitored for diazinon before and after the EPA ban on its residential uses. The total

number of samples having diazinon concentrations above the lower limits of detection significantly decreased from 2001 to 2004. The maximum and average concentrations, respectively, of diazinon detected each year were 2.58 and 0.32 µg/L in 2001, 1.67 and 0.10 µg/L in 2002, 1.91 and 0.06 µg/L in 2003, and 0.85 and 0.04 µg/L in 2004. These results indicate that the phasing out of residential uses of diazinon has led to a significant decrease in surface water occurrences.

Diazinon concentrations in water have also been monitored in the United States and in several Canadian studies associated with the use of the compound in agricultural applications. Kendall et al. (1993) monitored diazinon residues in ponds and creeks adjacent to a golf course in coastal Washington where two turf applications of diazinon were made at a rate of 2.2 kg active ingredient per hectare. A maximum diazinon residue of 17 µg/L was measured in the study area ponds and creeks. Wan et al. (1994) monitored concentrations of diazinon and six other organophosphate pesticides in farm ditches of the lower Fraser River Valley of British Columbia, Canada, from July to December 1991. These authors reported that diazinon was consistently found in ditch water (81% of samples) at 7 locations with a mean concentration of 0.07 µg/L (range of 0.01–0.34 µg/L). The percentage of positive detections for diazinon in water samples was 81%. The presence of diazinon in ditch water was correlated with consistent detection of diazinon residues in soils from nearby fields. Szeto et al. (1990) monitored the persistence of diazinon in coastal cranberry bogs and adjacent surface waters in British Columbia, Canada. Bogs were treated with two applications of diazinon 5G (granules) at a rate of 6 kg active ingredient per hectare approximately 2 weeks apart. One day after the first and second applications, maximum concentrations of diazinon in water in an irrigation ditch were 338 and 456 µg/L, respectively. Maximum concentrations in an adjacent reservoir were 78.5 and 58.1 µg/L for the first and second treatments, respectively. Water samples collected immediately outside the diked bog area contained a maximum of 29.1 µg/L diazinon, but concentrations were usually <10 µg/L. Tributary water 100 m downstream from the cranberry bog site contained a maximum diazinon residue of 2.8 µg/L. Li et al. (2002) monitored diazinon levels in water samples collected in June, August, and October 2000 from 13 agricultural water ditches in British Columbia, Canada near fields where diazinon was applied. Diazinon was found to range from not detected (<4 ng/L) to 259 ng/L, indicating that after application, high concentrations can reach local waterways. High diazinon concentrations, such as the 259 ng/L detection, may be of ecological relevance given that concentrations of 350 ng/L have been associated with toxic effects in aquatic organisms. Between March 1993 and May 1994, Gruber and Munn (1998) measured median and maximum diazinon concentrations of <0.002 and 0.018 µg/L, respectively, in Crab Creek Lateral, in which most of the flow is excess irrigation water, located in the Central Columbia Plateau in central Washington state. EPA's Water Resources Assessment for diazinon provided estimated environmental concentrations of diazinon

in surface water as a result of the highest label application rate on seven crop types calculated using the Pesticide Root Zone Model version 3.1 (PRZM) and Exposure Analysis Modeling System Version 2.97.5 (EXAMS) (EPA 1999). The peak and yearly average estimated environmental concentrations of diazinon ranged from 8.89 to 429 µg/L and from 1.61 to 58.7 µg/L, respectively.

Suzuki et al. (2003) monitored pesticide residues in rainwater from July 1999 to July 2000 at five sampling sites in Utsunomiya, eastern Japan. The annual deposited amount as an average value among the sampling sites for diazinon was 38.3 $\mu g/m^2$. In the 82 rainwater samples collected over the year, the maximum and mean concentrations of diazinon detected were 0.324 and 0.079 µg/L, respectively.

Recently, acute toxicity of sewage treatment plant effluents to aquatic bioassay testing organisms in the United States has been tied to diazinon (Amato et al. 1992; Burkhard and Jenson 1993). Given the considerable use of diazinon in urban areas, diazinon in sewage treatment effluents is not unexpected. Urban nonpoint source inputs from diazinon-impregnated yard wastes, runoff from treated lawn and garden areas, or illegal dumping may require increased pollution prevention efforts through the National Pollution Discharge Elimination System (NPDES) program in many larger cities (Amato et al. 1992; Burkhard and Jenson 1993). A maximum diazinon residue of 1.7 µg/L in POTW effluents was associated with the toxic fraction in effluent bioassay tests with *Ceriodaphnia dubia* (Burkhard and Jenson 1993). Amato et al. (1992) suggest that the significance of detecting diazinon at acutely toxic concentrations in municipal waste water may indicate a more widespread problem.

Schiff and Sutula (2004) detected diazinon in 93% of 128 storm-water runoff samples from eight different land uses over five storm events in urban southern California watersheds. The mixed agricultural land use had the highest flow-weighted mean diazinon concentration of 4,076.0 ng/L, followed by commercial and nursery agricultural land use with mean diazinon concentrations of 324.0 and 148.0 ng/L, respectively. High and low-density residential land use had mean concentrations of 99.2 and 67.6 ng/L, respectively, industrial land use had 89.6 ng/L, recreational land use had 63.2 ng/L, and the open space site had the lowest concentration of diazinon of <20 ng/L. Diazinon was detected in 100% of the samples collected at the mass emission sites Ballona Creek and Santa Monica Canyon, located in Santa Monica Bay, with flow-weighted mean concentrations of 242.9 and 452.3 ng/L, respectively.

In a groundwater contamination study of 28 of California's 58 counties that evaluated over 50 pesticides (from both point and nonpoint sources), diazinon was detected in 12 samples (Cohen 1986). Diazinon is included as an analyte of interest in the EPA Pesticides in Ground Water Database (EPA 1989) and was

detected at two sites. A detection in California was related to point source contamination (residue level was unspecified), and a detection of 478 µg/L (maximum) and 162 µg/L (mean) in Mississippi was in an area where appreciable agricultural use of pesticides occurs. In the Great Lakes region, diazinon was found in a survey of rural wells in southern Ontario, Canada, monitored between 1979 and 1984 (Frank et al. 1987) and in farm wells monitored between 1986 and 1987 (Frank et al. 1990b). However, no concentrations of diazinon in groundwater were provided by these authors. In the U.S. Geological Survey's National Water-Quality Assessment Program 1992–1996, 2,485 groundwater sites were sampled in 20 of the nation's major hydrologic basins were analyzed for 90 pesticide compounds (Kolpin et al. 2000). Diazinon was detected at a frequency of 1.30% at 2,459 sites with a maximum detected concentration of 0.16 µg/L.

Only limited data on the concentration of diazinon in drinking water are available since drinking water facilities are not required to monitor for diazinon (EPA 1999). EPA's Water Resources Assessment for diazinon provided a drinking water assessment and set the upper bound on the drinking water exposure estimate through modeling with surface and groundwater data (EPA 1999). The estimated diazinon acute exposures in drinking water were 2.3–22, 3.0–22, and 0.90 µg/L based on agricultural and non-agricultural use surface water and groundwater, respectively. The estimated diazinon chronic exposures in drinking water were 0.19–5.8, 0.46–5.8, and 0.90 µg/L based on agricultural and non-agricultural use surface water and groundwater, respectively. Eitzer and Chevalier (1999) detected diazinon in 5 of 53 residential drinking wells at an average concentration of 0.02 µg/L in a single town in south-central Connecticut which relies on groundwater for its potable water source. In the EPA's National Survey of Pesticides in Drinking Water, no diazinon was detected (limit of detection of 1.10 µg/L) in 1,349 wells (783 rural domestic wells and 566 community water system wells) randomly selected and sampled once for diazinon in 38 states (EPA 1999). In February 2005, the EPA's Office of Water added diazinon to the Drinking Water Contaminant Candidate List (EPA 2006j). EPA uses this list of unregulated contaminants to prioritize research and data collection efforts to help determine whether the specific contaminant should be regulated.

6.4.3 Sediment and Soil

Diazinon has not been the focus of many national soil or sediment monitoring programs in the United State, but has been monitored in regional studies associated with agricultural applications in both the United States and Canada. In a national surface water quality monitoring study (1976–1980), diazinon was detected in 0.5% of the sediment samples analyzed, with a maximum residue of 7.1 µg/L (Carey and

Kutz 1985). Domagalski and Kuivila (1993) reported concentrations of diazinon in suspended sediments from various sites from San Francisco Bay ranging from not detected to 2.8 ng/g.

Soil contamination of diazinon ranging from 95.5 mg/m^2 (2 hours post-application) to 35.6 mg/m^2 (342 hours post-application) resulted from spray applications of 4.5 kg diazinon (50 WP formulation) per hectare to a dormant peach orchard in the Central Valley of California (Glotfelty et al. 1990b). Diazinon concentrations in sediments of a cranberry bog treated with two applications of diazinon (Diazinon 5G at 6 kg active ingredient per hectare) were measured by Szeto et al. (1990). These authors reported that the highest diazinon residues were 21 µg/g (wet weight) in sediments of irrigation ditches collected 4 days post-application. The maximum sediment concentration measured in an adjacent reservoir was 2 µg/g. Four days post-application, the maximum sediment concentration was 80 µg/kg in a waterway outside the diked bog and only 10 µg/kg in a tributary 100 meters downstream from the bog. Wan et al. (1994) monitored ditch water, soils, and sediments from July to December 1991 in an agricultural area in the lower Fraser River Valley of British Columbia, Canada. Diazinon concentrations in ditch sediment were detected at three sites; the mean concentrations were 8, 2, and 38 µg/kg at the Vancouver, Cloverdale, and Sumas Prairie sites, respectively. Diazinon was also detected in topsoil (<5 cm deep) at five sites; the mean concentrations were 268 µg/kg (range of 2–3,307 µg/kg), 5 µg/kg (range of 1–9 µg/kg), 769 µg/kg (range of 13–2,862 µg/kg), 13 µg/kg (range of 4–30 µg/kg), and 39 µg/kg (range of 1–236 µg/kg) at the Westham Island, Ladner, Burnaby, Cloverdale, and Sumas Prairie sites, respectively. The concentrations at all these stations declined from July to December. Diazinon concentrations ranging from 0.5 to 5.4 ng/g dry weight were measured in sediments collected from the Salton Sea, an agricultural drainage reservoir in California, in 2000 and 2001 (Sapozhnikova et al. 2004). Sediment concentrations were 64% higher in 2001 than in 2000.

Sediment samples collected from six sites in the Petaluma River, Sonoma Creek, and Napa River, which feed into the San Pablo Bay, California contained diazinon concentrations ranging from 8.45 to 13.10 µg/kg (Baum et al. 2001).

6.4.4 Other Environmental Media

Braun and Frank (1980) reported diazinon residues in three fish species collected from a creek in southern Ontario, Canada, contaminated from a point source discharge. Tissue residues for the three edible fish species were 18 µg/g in the brown bullhead (Ictalurus nebulosus), 17 µg/g in the black crappie (*Pomoxis nigromaculatus*), and 92 µg/g in the gizzard shad (*Dorosoma cepedianum*). The maximum diazinon

concentrations measured in the contaminated creek water for 1975–1976 and 1976–1977 were 140 µg/L (5.75 µg/L mean) and 26 µg/L (1.02 µg/L mean), respectively. Sapozhnikova et al. (2004) reported diazinon residues in tilapia (*Tilapia mossambique*) and orange mouth Corvina (*Cynoscion xanthulu*) collected from the Salton Sea, an agricultural drainage reservoir in California, in May 2001. In the corvina, diazinon was found in the muscle, liver, gonads, and gills at mean concentrations of 5.4, 17.2, 6.2, and 3.6 ng/g wet weight, respectively. In the tilapia, diazinon was found in the muscle, liver, gonads, and gills at mean concentrations of 4.4, 8.8, 5.2, and 2.4 ng/g wet weight, respectively.

Concentrations of diazinon in ready-to-eat foods were monitored for 10 years from 1982 to 1991 through the FDA's Revised Market Basket Survey (KAN-DO 1995). Diazinon was detected in 894 samples of 144 different foods at a mean concentration of 0.0019 µg/g. In the EPA's Revised Organophosphate Pesticides Cumulative Risk Assessment, a summary of residue monitoring data on organophosphate pesticides in food for the years 1994–2000 was reported (EPA 2002). The detection of diazinon in these various foods and its concentration are presented in Table 6-3. The report also included a summary of FDA Total Diet Study analyses on organophosphate pesticides on meats for the years 1991–1999. The mean concentrations of diazinon residues found in meats (in mg/kg) were 0.0009 in beef steak, loin, pan-cooked, 0.0008 in pork chop, pan-cooked, 0.009 in lamb chop, pan-cooked, and 0.002 in lamb chop, pan-cooked (sample 2). Residues of diazinon in levels of 0.005–0.586 mg/L have been reported in milk (Salas et al. 2003).

The frequency of occurrence of diazinon detections in the FDA Total Diet Study was 9% in 1989 (FDA 1990), 6% in 1990 (FDA 1991), 4% in 1991 (FDA 1992), 5% from 1991 to 1993 (FDA 1994), 5% in 1994 (FDA 1995), 3% in 1995 (FDA 1996), 2.4% in 1996 (FDA 1998), and 2% in 2003 (FDA 2005b). Diazinon intakes in µg/kg body weight/day, estimated for the total diet analyses were 0.0031, 0.0034, and 0.0017 in 1989 (FDA 1990); 0.0026, 0.0022, and 0.0017 in 1990 (FDA 1991); and 0.0049, 0.0022, and 0.0022 in 1991 (FDA 1992) for 6–11-month-old infants, 14–16-year-old-males, and 60–65-year-old-females, respectively.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

While no quantitative information is available on the percentage of diazinon released to each environmental compartment, diazinon can be emitted to any or all environmental media (air, surface water, groundwater, and soil) depending on the source of the release, formulation used, and prevailing environmental conditions. In order to mitigate the exposure and risk to the general population, especially

Table 6-3. Diazinon Residues in Various Foods from 1994 to 2000

Food item	Number analyzed	Number of detections	Average concentration (ppm)[a]	Maximum concentration (ppm)
Apple juice	1,554	0	0	0
Apples	2,472	19	$1.2x10^{-4}$	0.12
Apples (single serving)	377	1	$1.9x10^{-5}$	0.007
Bananas	1,126	0	0	0
Broccoli	634	0	0	0
Cantaloupe	1,640	6	$4.7x10^{-5}$	0.024
Carrots	2,071	79	$6.8x10^{-4}$	0.086
Celery	176	8	$4.32x10^{-4}$	0.027
Cherries	275	2	$5.8x10^{-5}$	0.013
Corn syrup	454	0	0	0
Cucumbers	1,467	8	$1.51x10^{-4}$	0.083
Grape juice	1,378	0	0	0
Grapes	2,625	38	$3.04x10^{-4}$	0.15
Green beans (canned)	854	0	0	0
Green beans (fresh)	1,898	5	$6.18x10^{-4}$	1.1
Green beans (frozen)	743	11	$1.24x10^{-4}$	0.019
Lettuce	1,616	47	$3.82x10^{-4}$	0.16
Milk	1,366	0	0	0
Nectarines	345	0	0	0
Orange juice	1,392	0	0	0
Oranges	2,636	0	0	0
Peaches (canned)	754	0	0	0
Peaches (fresh)	1,623	97	$9.57x10^{-4}$	0.16
Peaches (single serving)	534	29	0.0012	0.23
Peanut butter	716	0	0	0
Pears (canned)	737	2	$4.9x10^{-5}$	0.018
Pears (fresh)	1,779	39	$3.56x10^{-4}$	0.094
Pears (single serving)	696	6	$2.28x10^{-4}$	0.084
Pineapples	364	0	0	0
Potatoes	1,770	1	$2x10^{-6}$	0.003
Poultry (adipose tissue)	476	2	$1.71x10^{-4}$	0.04542
Poultry (liver)	479	1	$2.4x10^{-5}$	0.011676
Poultry (muscle)	145	1	$1.34x10^{-4}$	0.01944
Soybean grain	748	8	$5.1x10^{-5}$	0.01
Spinach (canned)	863	0	0	0
Spinach (fresh)	1,638	40	$9.9x10^{-4}$	0.39
Spinach (frozen)	715	8	$1.17x10^{-4}$	0.024

Table 6-3. Diazinon Residues in Various Foods from 1994 to 2000

Food item	Number analyzed	Number of detections	Average concentration (ppm)[a]	Maximum concentration (ppm)
Strawberries (fresh)	1,768	16	$1.26x10^{-4}$	0.049
Strawberries (frozen)	155	0	0	0
Sweet bell peppers	1,468	20	$1.51x10^{-4}$	0.061
Sweet corn (canned)	652	0	0	0
Sweet corn (fresh)	19	0	0	0
Sweet corn (frozen)	635	0	0	0
Sweet peas (canned)	746	0	0	0
Sweet peas (fresh)	9	0	0	0
Sweet peas (frozen)	703	10	$1.82x10^{-4}$	0.049
Sweet potatoes	1,559	3	$8x10^{-6}$	0.007
Tomatoes (canned)	737	1	$7x10^{-6}$	0.005
Tomatoes (fresh)	1,962	12	$9.1x10^{-5}$	0.09
Wheat	1563	24	$2.39x10^{-4}$	0.028
Winter squash (fresh)	1,216	3	$2.1x10^{-5}$	0.015
Winter squash (frozen)	470	1	$1.5x10^{-5}$	0.007

[a]Nondetects were counted as zero in calculating the average.

Source: EPA 2002

children, the EPA has phased out all residential uses of diazinon as of December 2004 (EPA 2004b). General population exposure to diazinon may occur through three routes: dermal contact, inhalation, and ingestion of contaminated food or drinking water. Past major routes of exposure to diazinon for the general population were through dermal contact directly with the chemical during domestic application for control of home and garden pests; through dermal contact with diazinon-treated plant materials such as grass clippings; or through dermal contact with treated surfaces (e.g., furniture) in domestic or office buildings. For children particularly, potential sources of exposure were related to the indoor application of diazinon on furniture, rugs, and flooring and from translocation from pets. The general population may also be exposed to diazinon through inhalation of contaminated ambient (outdoor) air particularly in agricultural areas where diazinon is extensively used or in urban areas where it is applied to lawns and gardens. Since many commercial buildings and residential buildings were sprayed with diazinon or used pest control strips that vaporize diazinon, there has been the possibility of exposure from inhalation of vapors in these diazinon-treated indoor air spaces. The oral route of exposure may include ingestion of foods contaminated with small residues of diazinon or consumption of contaminated drinking water.

Davis et al. (1983) reported that dermal exposure (rate of contact with skin) to diazinon from spray applications of the compound for home and garden applications ranged from 5,700 to 29,000 µg/hour depending on the type of sprayer used. The mean respiratory exposures ranging from 1.9 to 7.4 µg/hour, were negligible compared to the dermal exposures. In addition, these authors reported that dermal exposure of the hands, which accounted for 85% or more of the total dermal exposure, could be easily reduced by the use of protective gloves.

Pesticides may be transported into homes by translocation of vapors and by track-in from outdoors on shoes, clothing, and animal fur. Factors such as the activities of children and pets might serve as an important vehicle for transport of diazinon into homes. Morgan et al. (2001) conducted a 15-day study in 1999 to investigate the potential for a family with an indoor/outdoor pet dog to transport diazinon into a home and the potential exposure to the residents following lawn application. Entryway deposits on the doormats had diazinon residue levels as high as 135.0 µg/g 3 days after application. Airborne levels in the living room of the home were at least 50 times above background levels at 0, 3, 9, and 15 days after application, with the highest concentration being 0.18 µg/m^3 the day of application. The living room carpet contained diazinon residues six times greater than background levels at concentrations of 4.28, 3.59, and 3.56 µg/g at 3, 9, and 15 days post-application. The dog had diazinon residues on its paws as high as 2.27 µg the day of application and 1.39 µg 3 days post-application, and also had residues as high as 0.47 µg/g on its fur. The data show that diazinon residues were being physically tracked in by the pet

and humans and also redistributed into the indoor air. A gradient of diazinon residues was found from the soil to the entryway and into the living room of the home. Also, the dog is shown to be a good vehicle for the uptake, transfer, and translocation into the home and is likely to expose the occupants through direct contact, such as petting and playing (Morgan et al. 2001).

A study conducted by Lewis et al. (2001) also demonstrated the importance of translocation of pesticides from areas of application to surfaces accessible for human contact and the potential exposure through inhalation, dermal contact, and ingestion. Potential indoor air inhalation exposures to diazinon after indoor application were estimated to be as high as 0.5 μg/kg/day. Multimedia sampling at a subset of homes in Arizona participating in EPA's National Human Exposure Assessment Survey was conducted in order to assess residential environmental exposure to pesticides (Gordon et al. 1999). Diazinon was found in 53% of the house dust samples at <0.02–50.5 $\mu g/m^2$; indoor air, 63%, <0.002–20.5 $\mu g/m^3$; hand wipes, 32%, <0.01–18.4 μg; and foundation soil (2.5 cm depth), 37%, <0.007–7 μg/g.

Non-occupational exposure to diazinon for residents of two U.S. cities (Jacksonville, Florida, and Springfield, Massachusetts) was studied over three seasons: summer 1986, spring 1987, and winter 1988 (Whitmore et al. 1994). The study focused primarily on inhalation exposures with primary environmental monitoring consisting of 24-hour indoor air, personal air, and outdoor air. For the population of Jacksonville, Florida, the mean diazinon concentration ranges were 85.7–420.7 ng/m^3 for indoor air, 1.1–13.8 ng/m^3 for outdoor air, and 89.0–321.6 ng/m^3 for personal air. For the population in Springfield, Massachusetts, mean exposures were much less. The diazinon concentrations were 2.5–48.4 ng/m^3 for indoor air, 8.2–9.2 ng/m^3 for outdoor air, and 1.4–10.1 ng/m^3 for personal air. The mean air exposure for diazinon in Jacksonville, Florida, was 1,380 ng/day, and dietary exposures were 590–1,140 ng/day. The mean air exposure estimated for Springfield, Massachusetts, was almost 10 times lower (158 ng/day), while the dietary exposure (586 ng/day) was equal to the low end of the range for the population of Jacksonville, Florida. In Jacksonville, Florida, characterized as a high pesticide use area, inhalation exposure exceeded dietary exposure; in Springfield, Massachusetts, characterized as a low pesticide use area, the dietary exposure to diazinon exceeded the inhalation exposure.

Workers employed in industries that manufacture, formulate, package, or apply diazinon and workers involved in the disposal of diazinon or diazinon-containing wastes have the potential to be exposed to the highest concentrations of diazinon. In occupational settings, dermal exposure and subsequent absorption through intact skin is the most important route of exposure, and inhalation exposure is generally less important (Jeyaratnam and Maroni 1994). Inhalation of diazinon depends on its volatility, the type of

formulation used, and the application technique employed. Occupational ingestion may occur as a result of poor work practices and/or lack of personal hygiene.

NIOSH recommends that the occupational exposure level not exceed 0.1 mg/m^3 for a 10-hour TWA workday (NIOSH 2006a). In addition, the American Conference of Governmental Industrial Hygienists has recommended a time-weighted average threshold limit value (TWA-TLV) of 0.01 mg/m^3 with a skin notation for occupational exposure to diazinon (RTECS 2006).

Except for professional pesticide applicators or farm workers, the exposure risks from diazinon appear relatively minor as long as label instructions are followed and safeguards are taken to avoid extensive dermal contact. Even studies of dermal exposure typical of shearers handling sheep that have been dipped in diazinon showed dermal absorption rates of <4% (Wester et al. 1993). Contamination was generally highest on the face, hands, and arms, while inhalation was a minor route of exposure as levels of diazinon were less than a third of the TWA occupational exposure limit (Nutley et al. 1995). Studies of dermal exposure for workers in grain elevators failed to detect diazinon in grain dust above the 0.01 μg/g detection limit, although much higher levels have been reported from Australia (Palmgren and Lee 1984).

The use of a 2-day lag period from the time of diazinon application to the use of office or domestic indoor space appears adequate to eliminate exposure risks from vapors and residues that might be incurred from either inhalation or dermal absorption. Air sampling of a room treated with 36 pest control strips measured a maximum diazinon air concentration of 1.34 μg/m^3 15 days post-application (Jackson and Lewis 1981). Similarly, Williams et al. (1987) found that air sampling in two animal facility areas used by facility personnel and treated monthly with a 1% aqueous diazinon solution measured 2–3 μg/m^3 <24 hours post-application. Currie et al. (1990) also measured diazinon air concentrations in empty and furnished offices treated with a 1% aqueous solution. Four hours post-application, diazinon air concentrations were 163 and 158 μg/m^3 in two empty offices and 28 μg/m^3 in the furnished office. One day post-application, diazinon levels in the offices ranged from 125 μg/m^3 (empty office) to 27 μg/m^3 (furnished office), but by 2 days post-application, the highest diazinon air concentration measured was 53 μg/m^3. Air sampling levels of diazinon 2 days post-treatment in these three indoor exposure contexts were well below the NIOSH 8-hour TWA permissible exposure level (PEL) of 100 μg/m^3.

Residual air concentrations of diazinon in a commercial greenhouse were studied by Lenhart and Kawamoto (1994). These authors monitored diazinon air concentrations applied as a spray and by cold

fogging. The 40-minute spray application was made to a portion of the greenhouse with only passive ventilation (adjustable window vents). During application, circulating fans were turned off and all roof vents were closed. After the spray application, 1.4 L of the diazinon emulsifiable concentrate formulation in 18 L of water was added to each of two cold fogging machines set for a 4-hour cold fogging application. Air samples were collected during the work shift prior to pesticide application, hourly during the application, and for 4 consecutive days after the pesticide application. Full shift area air samples were collected. During the post-application period, air circulating fans were continuously operated and the roof vents were open occasionally. The 8-hour TWA for the spray application ranged from not detected to 25 μg/m^3. The 8-hour TWA diazinon concentrations were 6.0–52 μg/m^3 (Saturday), 3–30 μg/m^3 (Sunday), 2.4–17 μg/m^3 (Monday), and not detected–12 μg/m^3 (Tuesday). During the cold fogging application, diazinon concentrations on Friday were 730–3,030 μg/m^3. Residual 8-hour TWA concentrations for this application were 70–250 μg/m^3 (Saturday), 27–67 μg/m^3 (Sunday), 20–59 μg/m^3 (Monday), and 19–40 μg/m^3 (Tuesday). Two of the 4 samples collected on Saturday exceeded the NIOSH TWA permissible exposure level of 100 μg/m^3 for occupational exposures to diazinon. Results of this study indicate that greenhouse workers can be at risk of inhalation exposure to residual diazinon concentrations. The authors believe that all diazinon applications should be conducted on Friday evenings after the greenhouse workers have left so that much of the residual pesticide can settle over the weekend.

Wright et al. (1996) conducted a study to determine the levels of insecticide residues in the ambient air of insecticide storage and office rooms in commercial pest control buildings. Diazinon was detected in the air of office rooms at levels of <0.01 to 0.36 and <0.01–0.13 μg/m^3 measured in summer and winter, respectively. In the air of the storage rooms, diazinon was detected at levels of <0.01–0.48 and <0.01–0.36 μg/m^3, respectively. The mean diazinon quantity detected in the ambient air of all company rooms in 38 air samples was 0.08 μg/m^3.

Finally, air sampling at a retail garden store conducted to determine exposures for retail employees showed levels of diazinon averaging only 3.4 μg/m^3, well below the NIOSH TWA exposure level of 100 μg/m^3 (Wachs et al. 1983). However, these authors point out that the air concentrations they reported may vary greatly among retail stores depending on the amounts and types of diazinon formulation sold, air temperature, condition of the packaging material (e.g., torn packaging, loose lids), prior spills, and types of floor coverings.

The National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that 39,342 workers (including 3,216 women) employed at 3,168 facilities were potentially exposed to diazinon in the United States (NIOSH 2006b). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace.

6.6 EXPOSURES OF CHILDREN

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

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

In areas where diazinon is sprayed for agricultural use, children within the general population are likely to be exposed to diazinon in the same ways as adults, including through contact with sprayed plants, soil, or other surfaces; breathing contaminated air; eating contaminated foods; or drinking contaminated water. Diazinon residues bound to soil or dust particles in carpets or on bare floors may present an exposure route for infants and toddlers through dermal contact or ingestion. Translocation from household pets exposed to diazinon may also present an exposure route through dermal contact or ingestion.

Several studies suggest that house dust is an important route of toxicant exposures to young children. In a study of pesticide exposure to children in the home in rural areas in California, samples of house dust were analyzed from a day care center and 10 homes, 5 of which were also the home of at least one farm worker (currently working in the field) and 8 of which reported home pesticide use (Bradman et al. 1997). Excluding nondetects, concentrations of diazinon ranged from 0.7 to 169 mg/kg in four farm-worker homes and from 0.2 to 2.5 mg/kg in three nonfarm worker homes. Diazinon was detected at 0.10 mg/kg in the daycare center. For children in two of the homes with the highest levels of diazinon, ingestion

exposures leading to risks for cholinesterase inhibition exceeded the EPA Office of Pesticide Program's chronic oral RfD of $9x10^{-5}$ mg/kg/day. The home with the highest level (169 mg/kg) also exceeded the EPA subchronic RfD of $9x10^{-4}$ mg/kg/day. Diazinon residues of 220, 125, and 52 ng were detected on the hands of 3 of the 11 toddlers; all 3 toddlers resided in a different farm worker home (Bradman et al. 1997). For the child with the highest diazinon level on the hands, exposures leading to risks of cholinesterase inhibition due to diazinon ingestion from hand residues also exceeded the chronic RfD (Bradman et al. 1997).

The Minnesota Children's Pesticide Exposure Study (MNCPES) monitored house dust levels from carpets and other surfaces and hand rinses for 102 children, ages 3–13, over a 1-week sampling period (Lioy et al. 2000). Diazinon was detected in approximately 10% of carpet and surface samples collected. A different collection method yielded eight samples with detectable quantities (detection limit of 0.076 ng/cm^2 surface) out of 194 samples collected. It was only detected in 6 of 94 hand rinse samples collected. Seventy-five percent of the children had played on the floor and 67% had played outside between hand rinse samples, increasing their exposure to diazinon present on carpets and other surfaces.

Inhalation exposure to semivolatile pesticides in indoor air can be substantial and may be a primary route of exposure after residential use among homes using insecticides. However, an aggregate-exposure study of pesticides, including diazinon, among 102 children in Minnesota concluded that ingestion was by far the dominant route of exposure when compared to inhalation (Clayton et al. 2003). EPA regulatory action to phase out residential and some agricultural use of diazinon has been successful at reducing indoor air exposure in residential homes (EPA 2004b; Whyatt et al. 2004).

Children may be exposed to diazinon and its residues in the foods that they eat. In the FDA Total Diet Study for infants and toddlers conducted between 1980 and 1982, the average concentration and the calculated average daily intake of diazinon in different food groups were determined (Gartrell et al. 1986). In the infant diet, the average concentrations (mg/kg) and average daily intakes (µg/day) of diazinon by food group were 0.0002 and 0.0148 in meat, fish, and poultry, 0.0051 and 0.245 in grain and cereal products, and 0.0001 and 0.0016 in oils and fats, respectively. In the toddler diet the average concentrations (mg/kg) and average daily intakes (µg/day) of diazinon by food group were 0.0002 and 0.0230 in meat, fish, and poultry, 0.0034 and 0.387 in grain and cereal products, 0.0004 and 0.0268 in vegetables, 0.0001 and 0.0157 in fruit and fruit juices, 0.0007 and 0.0114 in oils and fats, and 0.0003 and 0.0073 in sugar and adjuncts, respectively. Data on the weight-adjusted intake of diazinon by infants and toddlers were determined based on the results of the FDA Total Diet Studies for fiscal years 1978–

1981/1982 (Gartrell et al. 1986). The reported weight-adjusted intakes of diazinon ranged from 0.002 to 0.032 µg/kg body weight/day for infants and 0.004–0.034 µg/kg body weight/day for toddlers for the study years.

Quantitative estimates of the exposure of infants and children to pesticides have been reported in the results of FDA Total Diet Studies conducted in the 1980s using the amounts of pesticide residues in foods thought to be in the diets of infants or children. Estimates of the mean intake of diazinon per unit body weight were made for the 6–11-month-old age group, 2-year-old age group, and the 14–16-year-old female and 14–16-year-old male age groups. For the period June 1984–April 1986, the estimates were 0.0020 µg/kg/day for the 6–11-month-old group, 0.0047 µg/kg/day for the 2-year-old group, 0.0018 µg/kg/day for the 14–16-year-old female group, and 0.0025 µg/kg/day for the 14–16-year-old male group (Gunderson 1995a). For the period July 1986–April 1991, the mean daily intake estimates were 0.0061 µg/kg/day for the 6–11-month-old group, 0.0106 µg/kg/day for the 2-year-old group, 0.0037 µg/kg/day for the 14–16-year-old female group, and 0.0052 µg/kg/day for the 14–16-year-old male group (Gunderson 1995b). Diazinon residues were not detected in any of the samples of infant formula (milk-based without iron, canned, ready-to-serve) analyzed in the study (Gunderson 1995b).

In the FDA regulatory monitoring of domestic foods that may be eaten by infants/children conducted from 1985 to 1991, the maximum residue concentrations of diazinon detected were 0.46 mg/kg in apples, 0.17 mg/L in whole milk, 0.26 mg/kg in oranges, 0.06 mg/kg in pears, and trace amounts in bananas (Yess et al. 1993). In imported foods, the maximum residue concentrations of diazinon were 0.06 mg/L in apple juice, 0.08 mg/kg in apples, 0.11 mg/kg in pears, and trace amounts in bananas. In the FDA Total Diet Study of infant foods conducted over the period 1985–1991, diazinon was detected at a maximum residue concentration of 0.0004 mg/kg in infant mixed cereal, dry, prepared with whole milk, 0.0004 mg/kg in beef, high meat, and vegetables, 0.0006 mg/kg in vegetables with bacon/ham, and 0.0009 mg/kg in vegetables with beef (Yess et al. 1993). The maximum diazinon residue concentrations detected in adult foods eaten by infants/children reported in this study were 0.002 mg/kg in apples, red, with peel, raw, 0.004 mg/kg in peanut butter, creamy, and 0.005 mg/kg in pears, raw.

Based on a calculated acute population adjusted dose (aPAD), at which no adverse health effects would be expected using the safety factor prescribed in the Food Quality Protection Act (FQPA), the population subgroup with the highest acute dietary exposure (at 63% of the aPAD) and the highest chronic dietary exposure (at 22% of the cPAD) is children aged 1–6 (EPA 2004b). However, values of <100% of the

aPAD or cPAD are considered to be not of concern (EPA 2004b). The reported aPAD and cPAD values were 0.0025 mg/kg/day (2.5 µg/kg/day) and 0.0002 mg/kg/day (0.2 µg/kg/day), respectively.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Other than individuals who are occupationally exposed to diazinon (during its production, formulation, packaging, distribution, use, or disposal), populations exposed to higher than background concentrations of diazinon in ambient air include those living near chemical manufacturing or processing sites, individuals living on farms or in the vicinity of agricultural areas where diazinon is extensively used, and individuals living near hazardous waste sites. Individuals living near these sites may also be exposed to potentially higher concentrations of diazinon or its metabolites in their drinking water if they obtain tap water from wells located near these sources. Children may receive higher diazinon doses from dermal exposures if they play on freshly treated lawns or soil. In addition, children may receive potentially higher oral doses from ingestion of diazinon-treated soils from their hands while playing in contaminated areas. In order to mitigate the exposure and risk to the general population, especially children, the EPA has phased out all residential uses of diazinon as of December 2004 (EPA 2004b).

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

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. While the principal properties of diazinon are well characterized, (Howard 1991; HSDB 2008; NIOSH 2005; O'Neil et al. 2001) there are data gaps for melting point, odor and taste thresholds, autoignition temperature, and explosive limits for the compound. However, these properties are sufficient in assessing the compound's environmental fate. There are also data gaps for some spontaneously-produced degradation products, some of which may be as toxic as, or more toxic than, diazinon.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2005, became available in May of 2007. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Diazinon is commercially produced in the United States and abroad. Production in the United States was estimated to be 2.63 million kg in 1982 (HSDB 2008) and 4.67 million kg in 1990 (Larkin and Tjeerdema 2000). Recent production volume data were not located. As of June 30, 2001, manufacturing of indoor use products containing diazinon was discontinued. Manufacture of non-agricultural outdoor use products containing diazinon was discontinued as of June 30, 2003 (EPA 2004b). Production amounts of diazinon should decrease due to the discontinuation of all residential products containing this chemical. Limited data were found on import volumes; an estimated 6.41×10^4 kg diazinon was imported into the United States in 1982 (HSDB 2008). The United States exported an estimated 5.8 million pounds of diazinon from 1997 to 2000 (Smith 2001).

Diazinon is used in agriculture as an insecticide on a variety of crops. It was formerly used extensively in home and garden applications, such as in pest strips and on turf. Due to the emerging health and ecological risks posed by diazinon, manufacturers agreed to phase out and cancel all residential products. As a result, after December 31, 2004, no diazinon products with residential uses would be registered or sold (EPA 2004b). For 1987 through 1997, total annual domestic usage of diazinon was over 13 million pounds. However, most of this (about 70%) was allocated to outdoor residential uses (EPA 2004b). Since residential uses of diazinon have been discontinued, the total annual usage should be significantly lower. Approximately 4 million pounds of active ingredient diazinon are used annually on agricultural sites (EPA 2004b).

For ultimate disposal, large amounts of diazinon residuals should be incinerated in a unit with effluent gas scrubbing, while physical, chemical, and biological treatments may be appropriate for disposal of smaller quantities of diazinon. Composting has also been used for the disposal of diazinon-contaminated soils and organic solids (Felost et al. 2003).

Environmental Fate. Diazinon is moderately mobile in some soil types (Arienzo et al. 1994; Kenaga 1980; Sharom et al. 1980a). Information on the mobility of diazinon and on a major degradation product 2-isopropyl-6-methyl-4-hydroxypyrimidine in various soil types is available (Arienzo et al. 1994; Levanon et al. 1994; Sharom et al. 1980a; Somasundaram et al. 1991). In the atmosphere, diazinon is subject to degradation due to photolysis (Gore et al. 1971) and reactions with hydroxyl radicals (Glotfelty et al. 1990a; Meylan and Howard 1993; Schomburg et al. 1991; Seiber et al. 1993). In water, diazinon is subject to hydrolysis, photolysis and biodegradation. The rate of degradation of diazinon in water and soil is strongly influenced by pH (Chapman and Cole 1982; Ferrando et al. 1992; Frank et al. 1991b; Garcia-Repetto et al. 1994; Sharom et al. 1980b). Diazinon undergoes only slight photolysis in water, with reported half-life estimates ranging from 42 to 88 days (EPA 1976; Frank et al. 1991b). Diazinon can be degraded at the soil surface by photolysis (Burkhard and Guth 1979), and in soils and sediment by hydrolysis (Chapman and Cole 1982; Levanon et al. 1994; Schoen and Winterlin 1987; Sethunathan and MacRae 1969; Somasundaram et al. 1989, 1991) and by biodegradation by microorganisms (Adhya et al. 1981; Barik and Munnecke 1982; Gunner and Zuckerman 1968). Additional information on the mechanism by which diazinon is converted to diazoxon in the atmosphere would be useful; additional information on the persistence and mobility of the major degradation products of diazinon would also be useful in evaluating the environmental fate of diazinon and its degradation products.

Bioavailability from Environmental Media. Diazinon can be absorbed following inhalation, dermal, or oral exposures. Absorption through the skin is of major concern for exposures of farmers, farm workers, commercial applicators, or homeowners related to the use of diazinon as an insecticide or nematocide (Davis et al. 1983). Absorption via inhalation is a major concern particularly with respect to indoor exposures to diazinon within 2 days post-application of the compound as a pest control agent in commercial buildings and homes (Currie et al. 1990; Jackson and Lewis 1981; Lenhart and Kawamoto 1994; Williams et al. 1987). Additional information on the concentrations of diazinon in indoor air and in groundwater from domestic wells, particularly from environments near hazardous waste sites, is needed to determine the bioavailability of diazinon in these media.

Food Chain Bioaccumulation. Diazinon has an estimated low bioconcentration potential (BCF=77) (Kenaga 1980) in aquatic organisms, which is generally confirmed by measured BCF values obtained from laboratory studies with fish and other aquatic invertebrates (El Arab et al. 1990; Keizer et al. 1991; Sancho et al. 1993; Tsuda et al. 1989, 1995). Further information on measured BCF values for additional edible fish and shellfish would be helpful, as would information on tissue residues of diazinon and its major degradation products in edible species. No information was found on studies associated with plant uptake, but diazinon is rarely detected above EPA tolerance limits (Hundley et al. 1988). Bioaccumulation in aquatic food chains does not appear to be important, and no further information on biomagnification is required.

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

Diazinon is distributed in all environmental media and has been detected in ambient air (Carey and Kutz 1985; Glotfelty et al. 1990a; Kutz et al. 1976; Lewis and Lee 1976; Schomburg et al. 1991; Seiber et al. 1993; Zabik and Seiber 1993), in indoor air (Currie et al. 1990; Jackson and Lewis 1981; Lenhart and Kawamoto 1994; Palmgren and Lee 1984; Wachs et al. 1983; Williams et al. 1987), surface water (Braun and Frank 1980; Carey and Kutz 1985; Domagalski and Kuivila 1993; Frank and Logan 1988; Frank et al. 1990a; Kendall et al. 1993; Maguire and Tkacz 1993; Pereira and Hostettler 1993; Szeto et al. 1990; Wan et al. 1994), groundwater (Cohen 1986; EPA 1989), sediment (Carey and Kutz 1985; Domagalski and Kuivila 1993; Szeto et al. 1990), and some fish (Braun and Frank 1980). The levels of diazinon in air, surface water, groundwater, and soil have been well documented. Additional information on tissue residues of diazinon and its major degradation products in edible fish and shellfish species would be particularly helpful in quantifying health risk from consumption of contaminated species.

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

Exposure Levels in Humans. Data regarding levels of diazinon in humans from environmental exposures (the general population, populations living near hazardous waste sites, or occupationally exposed groups) are not available. It is arguable that these levels are not knowable because of the rapid metabolism and clearance of diazinon after it enters the body (Iverson et al. 1975; Machin et al. 1975; Mount 1984; Műcke et al. 1970). Additional studies which associate levels of diazinon in the environment and levels of diazinon metabolites in body tissues would be helpful. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. The exposure of children to diazinon through food ingestion has been estimated fairly extensively for various age groups, including infants, toddlers, and teenagers (Gunderson 1995a, 1995b; Yess et al. 1993). Weight-adjusted intakes for these age groups have also been calculated (Gartrell et al. 1986). Studies have also been conducted to assess the extent of exposure of children to diazinon through dermal contact, inhalation, and ingestion of environmental residues (Bradman et al. 1997; Clayton et al. 2003). Data on the body burden measurements of diazinon are needed to determine exposures to children living in both agricultural and non-agricultural areas. In order to assess exposures to nursing infants, studies of breast milk contamination would be useful.

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

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2006) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1.

Researchers at the Agricultural Research Service are conducting a study funded by the U.S. Department of Agriculture (USDA) to develop watershed management systems that increase productivity and improve

water quality and ecology in the Mississippi Delta. Best Management Practice studies will be coupled with research regarding the response of aquatic organisms to potential agricultural contaminants in order to improve development of Total Maximum Daily Loads.

Researchers at the University of California are conducting a study funded by the USDA to develop a pesticide transport model to characterize the vulnerability of surface and subsurface environments to pesticide contamination. The study will quantify the migration of pesticides through soils, aquifiers, and surface streams by taking into account physical, chemical, and biological processes and evaluate the potential threat of pesticides and their breakdown products to surface and subsurface systems. The model will then be applied to basins in the Sacramento-San Joaquin River and comprehensive management schemes will be identified.

Scientists at the University of California are conducting research funded by the USDA to assess the fate of hazardous chemicals in aquatic environments and their toxicity to resident organisms. The goals of the study are to characterize the dissipation and transformation processes in aquatic systems for pesticides, including diazinon, of current importance and to characterize the sublethal actions of pesticides in aquatic organisms.

Researchers at Michigan State University are conducting a study funded by the USDA to mitigate crop and turf damage caused by the Japanese beetle and the European chafer in Michigan, and ultimately in the north central United States, through host plant resistance and introduction of natural enemies. One of the objectives of the study is to find an alternative to diazinon for fall and spring control of the European chafer.

7. ANALYTICAL METHODS

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

Diazinon is widely used for agricultural purposes, which may result in human exposure during application, and residues on or in foods can result in exposure of humans by ingestion. Although all indoor and outdoor residential use has been phased out and cancelled, additional exposure potentials exist as a result of home gardening activities and pet pest control. Consequently, methods for the determination of diazinon in biological samples can be used to verify that exposure and absorption has occurred. Since diazinon is rapidly metabolized, determination of the parent compound can only provide evidence of very recent exposures (see Chapter 3). Methods have been reported for metabolites, and these are briefly discussed below and under Biomarkers of Exposure. Table 7-1 lists the applicable analytical methods for determining diazinon and its metabolites in biological fluids and tissues.

The principal method used for the detection of diazinon or its metabolites in biological samples is gas chromatography (GC) using a flame photometric detector (FPD), a mass spectroscopy detector (MS), an electron capture detector (ECD), or a flame ionization detector (FID). The preparation of samples usually involves variations of solid-phase extraction (SPE), and/or liquid/liquid extraction with organic solvents.

Garcia-Repetto et al. (2001) reported a method for diazinon identification and quantification in human blood using SPE, GC-nitrogen phosphorus detection (NPD) analysis followed by GC-MS confirmation. The average recovery of diazinon in blood is 87.92%, which is in the acceptable range established by the EPA. The limit of detection (LOD) and the limit of quantitation (LOQ) reported in the study are 1.97 and 6.58 μg/L, respectively. This method has improved a previous method that involved liquid-liquid

Table 7-1. Analytical Methods for Determining Diazinon and Transformation Products in Biological Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human blood	Addition of 1 mg/L azobenzene, 0.2 g ammonium sulfate and 2 mL 0.1 M sulfuric acid to a 0.5 mL sample of blood. Mixture is sealed and heated in a vial. Samples are collected by HS-SPME.	GC/MS	0.01 µg/g	Absolute recovery compared to a methanolic solution: 2.9%	Musshoff et al. 2002
Human fatty tissue (from greater omentum)	Tissue pulverization and extraction with acetone. Concentration and purification by sweep co-distillation and Florisil/anhydrous sodium sulfate column chromatography. Elution with 20% ether in hexane followed by hexane. Addition of internal standard.	GC/NPD	No data	No data	Kirkbride 1987
Human adipose, bile, blood, brain, stomach contents, kidney, and liver	Maceration of 0.5 g sample in tissue grinder with acetonitrile. Addition of aqueous sodium sulfate and partitioning into hexane. Concentration and clean up using Florisil column.	GC/ECD; GC/FID	No data	No data	Poklis et al. 1980
Human urine (DEP, DETP)	Dilution of urine with acetonitrile, azeotropic distillation for water removal, evaporation of solvent, redissolution in acetone and derivatization using penta-fluorobenzyl bromide.	GC/FPD	DEP: 0.072 ppm; DETP: 0.041 ppm	DEP: 96 (4.7% RSD); DETP: 99 (2.4% RSD) at 0.8 ppm	Reid and Watts 1981
Human urine (2-isopropyl-6-methyl-4-pyrimidinol)	Solid phase extraction with or without liquid/liquid partitioning.	GC/MSD	0.01 ng	101.3% for SPE alone; 100.8% for partitioning and SPE	Yokley et al. 2000
Human urine (2-isopropyl-6-methyl-4-pyrimidinol)	Hydrolysis with ∃-glucuronidase, solid phase extraction, liquid/liquid extraction, and evaporation.	HPLC-MS/MS	0.2 ng/mL urine	116% low dose; 93% high dose	Olsson et al. 2003
Bovine liver, rumen content (partially digested grain and vegetation mixture)	Extraction of homogenized sample with methanol-dichloromethane (10–90, v/v) followed by gel permeation chromatography and silica gel solid phase extraction clean-up.	GC/FPD	0.01–0.05 µg/g using 5 g sample	Rumen content: 95 (3% RSD) at 0.1 µg/g; liver: 88 (5% RSD) at 0.05 µg/g	Holstege et al. 1991

Table 7-1. Analytical Methods for Determining Diazinon and Transformation Products in Biological Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Animal fat	Sweep codistillation, Florisil clean up-elution with methylene chloride-light petroleum-acetonitrite (50:48.5:1.5).	GC/FPD	No data	90 (6% RSD) at 0.4 mg/L	Brown et al. 1987

[a]Diazinon is the target analytes unless otherwise specified.

DEP = O,O-Diethyl phosphate; DETP = O,O-Diethyl phosphorothionate; ECD = electron capture detector; FID = flame ionization detector; FPD = flame photometric detector; GC = gas chromatography; HPLC = high-performance liquid chromatography, HS = head space, MS = mass spectrometry; MS/MS = tandem mass spectrometry, MSD = mass selective detection; NPD = nitrogen phosphorus detector, RSD = relative standard deviation; SPE = solid-phase extraction; SPME = solid-phase microextraction

extraction with *n*-hexane and benzene resulting in more complex chromatograms. Not only is the method more precise, it also eliminates hazardous waste emissions and exposure of technicians to toxic solvents.

A method for the determination of diazinon in human serum has been published by researchers at the Centers for Disease Control and Prevention (Liu et al. 1994) in which 2-dimensional chromatography was used to determine 15 pesticides in 4 minutes. Supercritical fluid extraction (SFE) was used to recover pesticides into methylene chloride and this extract was analyzed using two 2-meter columns connected by an on-column thermal desorption modulator. Sensitivity for diazinon was reported to be 1.8 pg on-column; no details about overall recoveries were provided (Liu et al. 1994).

Yokley et al. (2000) developed a method for valid, precise, and accurate determination of the metabolite, 6-methyl-2-(1-methylethyl)-4(1H)-pyrimidinone (G-27550), of diazinon in urine. The sample can be prepared by SPE with an LOQ of 1.0 µg/L, or by SPE in conjunction with liquid/liquid partitioning (LOQ of 0.50 µg/L). Average recoveries of G-27550 for each sample preparation method are 101.3 and 100.8%, respectively. The final analysis was done by GC/mass selective detection (MSD). The LOD for G-27550 was 0.01 ng. The report states that this is an accurate Good Laboratory Practice (GLP)-validated method that may be used as a biomonitoring tool to determine potential diazinon exposure in humans (Yokley et al. 2000).

A method for the rapid quantification of diazinon metabolite 2-isopropyl-6-methyl-pyrimidin-4-ol in human urine using liquid chromatography/electrospry ionization-tandem mass spectrometry has been published (Olsson et al. 2003).

Diazinon was determined in bovine liver and rumen content by GC/FPD by Holstege et al. (1991) using a method with an LOD reported to be 0.01–0.05 µg/g using a 5-g sample. Recoveries were reported to be 95% from rumen content and 88% from liver. Brown et al. (1987) used GC/FPD and sweep codistillation to determine diazinon in animal fat. The recovery was stated to be 90% (6% relative standard deviation [RSD]) at 0.4 ppm; no LOD information was given (Holstege et al. 1991).

7.2 ENVIRONMENTAL SAMPLES

Table 7-2 lists the methods used for determining diazinon and some of its degradation products in environmental samples. The principal separation and detection methods of diazinon and degradation products in environmental samples include GC or high performance liquid-chromatography (HPLC), in

Table 7-2. Analytical Methods for Determining Diazinon and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air, gloves (surrogate for dermal exposure)	Preconcentration from air sample using PUF. Soxhlet extraction of PUF or gloves with 5% ethyl ether/hexane. Addition of deuterated internal standards and concentration using K-D and nitrogen blowdown.	Capillary GC/MS (can use multiple ion detection)	55 ng/m^3 (5.5 m^3 sample)	73% (14% RSD)	Hsu et al. 1988
Air (diazinon, diazoxon)	Preconcentration using ORBO-42 pesticide adsorbent tubes (Supelco). Extraction with acetone, evaporation just to dryness and redissolution in 100 µL acetone containing internal standard.	Capillary GC/NPD	No data	90% at 0.1% and 1 µg/m^3 (diazinon)	Williams et al. 1987
Air	Preconcentration of pesticide onto OVS-2 tube (13 mm quartz filter, XAD-2, 270 mg/140 mg. Elution with 90% toluene/10% acetone.	GC/FPD (NIOSH Method 5600)	0.0004 mg/m^3 (400 ng/m^3) for 120 L sample.	94% (2.7% RSD at 2.4 µg (0.01 µg/m^3, 240 L sample)	NIOSH 1994
Air	Air is drawn through a glass tube with a glass fiber filter and XAD-2 adsorbent. The samples are desorbed with toluene.	GC/FPD	3.0 µg/m^3	91.2%	OSHA 1986
Drinking water	Preconcentration onto 5 µm C_{18}-silica or 7 µm polystyrene-divinyl benzene co-polymer with subsequent backflush onto analytical HPLC column.	RP-HPLC/UV (254 mn)	0.03–0.06 µg/L (ppb)	91% (±10% RSD) at sample volumes up to 300 mL	Driss et al. 1993
Ground-water and finished drinking water	Extraction with methylene chloride. Drying and concentration of extract then resolution in MTBE.	GC/NPD	0.13 µg/L	94% (18% RSD)	EPA 1995b
Drinking water, river water	Preconcentration of 2.5 mL water onto C_{18} extraction disks, rinsing with additional 1 mL and purging disk with gas to remove residual water. Elution with ethyl acetate directly onto GC pre-column with solvent venting.	GC/NPD	Tap water: 20 pg/mL; river water: 20–50 pg/mL	>95% (<4% RSD at 200 ppt)	Kwakman et al. 1992

Table 7-2. Analytical Methods for Determining Diazinon and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Pond water	Micro liquid-liquid extraction of 1.5 mL water with 1.5 mL methyl t-butyl ether; 500 µL of extract slowly introduced into GC pre-column with solvent venting.	cap. GC/FPD	0.02 µg/L	102% (5% RSD) at 0.50 µg/L level	van der Hoff et al. 1993
Surface water	Adsorption of pesticides from 2 L of water onto XAD-2 and XAD-7 resins. Elution with methylene chloride, water removal and use of K-D to reduce volume.	GC/chemical ionization ion trap MS	0.0005 µg/L	103.8% (14% CV) at 1 ppb level	Mattern et al. 1991
Raw water and finished drinking water	SPE then elution under vacuum with ethyl acetate and dichloromethane. The extract is dried and concentrated.	GC/MS	0.015 µg/L	101% (3% RSD)	EPA 2000b
Finished drinking water, source water, or drinking water in any treatment stage	LSE followed by extraction with ethyl acetate and methylene chloride then evaporation of solvent.	GC/MS	0.11 µg/L	83% (9% RSD)	EPA 1995a
Filtered waste water and natural-water samples	Filtration of field samples using glass-filter fibers and SPE. Elution of dry SPE cartridges with dichloromethane and diethyl ether (4:1) followed by gentle evaporation of extract.	GC/MS	0.07 µg/L	93% (4% RSD)	USGS 2002b
Water	Filtration using glass-fiber filters followed by SPE. Elution of dry SPE columns with ethyl acetate then evaporation.	GC/FPD	0.01 µg/L	88% (16% RSD)	USGS 2002c
Water	Filtration of 1 L of water followed by extraction 3 times with 100 mL methylene chloride after addition of 20 g sodium sulfate. Concentration using K-D and solvent exchange to benzene. Concentrations done under nitrogen. Fractionation by HPLC.	GC/FPD (P-mode)	0.025 µg/L	92% (2% RSD)	Seiber et al. 1990

Table 7-2. Analytical Methods for Determining Diazinon and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	SPME of filtered water sample; thermal desorption of diazinon from SPME fiber.	GC/AED	1 µg/L with carbon line (193 nm); 3 µg/L with S line (181 nm)	No data (precision 8–12 relative standard deviation)	Eisert et al. 1994
Water	Extraction of analytes from water using SPE; elution with ethyl acetate (108 µL) directly onto retention gap with solvent venting.	GC/AED	1 ng/L (100 mL sample) with P channel	105% (4% RSD) at 5 µg/L	Hankemeier et al. 1995
Industrial and municipal waste water	Extraction of 1 L of sample with 60 mL methylene chloride 3 times. Water removal from extract and solvent exchange to hexane during K-D concentration.	GC/FPD or thermionic detection (P-mode); GC/MS for qualitative identifications recommended. (Method 1657)	0.6 µg/L	67% (6% RSD)	EPA 1993a
Waste water	Extraction of 1 L of water with 15% methylene chloride in hexane using a separatory funnel. Concentration using K-D. Cleanup (if needed) by Florisil fractionation or acetonitrile partition.	GC/FPD (P-mode) or GC/thermionic detection. GC/MS for qualitative compound identification recommended. (Method 614)	0.012 µg/L	94% (5.2% RSD)	EPA 1993b
Water	Direct injection or liquid/liquid extraction and concentration.	HPLC/UV	0.5 mg/L (direct injection); 0.5 µg/L (liquid/liquid extraction)	No data	Mallet et al. 1990
Bed sediment (lake and stream), aqueous suspended sediment and soil	Extraction with Soxhlet apparatus of minimum 25-g equivalent dry-weight samples using 350 mL dichloromethane and 25 mL methanol (93:7). Concentration and filtration of extract. Elution with dichloro-methane through chromato-graphic column. Concentration and resolution in ethyl acetate.	GC/FPD	1.24 ppb	71% (7% RSD)	USGS 2002d

Table 7-2. Analytical Methods for Determining Diazinon and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil (diazinon, diazoxon, 2-isopropyl-4-methyl-6-hydroxy-pyrimidine)	Extraction of soil with hexane:acetone (1:1), centrifugation, separation of hexane from acetone/water layer. Extraction of acetone/ water phase with chloro-form:diethyl ether (1:1), solvent exchanged to methanol. Hexane layer contained diazinon, chloroform/diethyl ether fraction contained 2-isopropyl-4-methyl-6-hydroxy-pyrimidine.	TLC	No data	No data	Sethunathan and Yoshida 1969
Soil (diazinon, 2-isopropyl-4-methyl-6-hydroxy-pyrimidine)	Sequential Soxhlet using acetone then methanol.	GC, TLC, GC/MS	No data	No data	Burkhard and Guth 1979
Water, soil	*Water:* Addition of deuterated standards to 1 L water and extraction 3 times with 200 mL methylene chloride. Water removal with anhydrous sodium sulfate then concentration using K-D and nitrogen blowdown. *Soil:* Addition of 10 mL water and deuterated standards to 50 g of soil followed by equilibration for 1 hour. Sonication 3 times with acetone/hexane. Phase separation followed by water removal using sodium sulfate, concentration using K-D, and nitrogen blow-down. Spiking with phenanthrene-d_{10} before analysis.	GC/MS (SIM)	100–200 ppt for water, 2–4 ppb for soil	Water: 89.4% (4.4% RSD) at 1 ppb Soil: 103% (15% RSD) at 20 ppb	Lopez-Avila et al. 1985
Cucumber, lettuce, grapes	Chopping of produce and extraction with acetone/ methylene chloride/petroleum ether (1:1:1). Evaporation to dryness and redissolution in acetone and concentration.	SFC/NPD	No data	No data	Zegers et al. 1994a

Table 7-2. Analytical Methods for Determining Diazinon and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Green beans, lettuce, carrot, bell pepper	Homogenization of produce with acetonitrile. Addition of NaCl to affect phase separation, removal of acetonitrile, water removal volume reduction, addition of deuterated internal standards.	GC/MS	50 ppb	88% (17% RSD)	Liao et al. 1991
Kale, endive, carrots, lettuce, apples, potatoes, strawberries	Extraction of crops with ethyl acetate and granular sodium sulfate, filtration, concentration with K-D. Sweep co-distillation cleanup for GC.	GC thermionic detector	No data for GC	No data	AOAC 1990a
Numerous non-fatty crops	Extraction with acetonitrile and partition into petroleum ether. Concentration using K-D and purification using Florisil column chromatography.	GC/KCl thermionic detector; identifications by combin-ations of gas, thin layer, and paper chroma-tography; polarographic confirmatory method	Polarographic method: 0.2 ppm based on 1 g crop in 1 mL cell	80%	AOAC 1990a, 1990b, 1990c
Soybeans and rice	Grinding of 25 g samples and extraction with 150 mL of 2:1 acetone: methanol; filtration and reduction of volume to 100 mL. Addition of water, NaCl followed by extraction with methylene chloride (2x); solvent evaporation and redissolution in methylene chloride:cyclohexane (1:1) and fractionation on Bio-Bead S-X3. Evaporation under N_2 stream and redissolution in 2 mL hexane.	GC/NPD or GC/MS (SIM)	Rice: 0.01 ppm soybeans: 0.05 ppm	Rice: 83.4% (1.5% RSD) at 1 ppm soybeans: 62.7% (8.6% RSD) at 1 ppm	Hong et al. 1993
Sweet cherries for baby food	Extraction with methylene chloride and cleaning with quaternary aminesilane-silica-dichloromethane.	GC/electron capture detection/ FPD and GC/NPD/ FPD	30 ppt	≥70% at 0.01 ppm	Bicchi et al. 1997

Table 7-2. Analytical Methods for Determining Diazinon and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Strawberries and cherries	Spike samples were sliced and homogenized.	HS-SPME	8.4 ppb in strawberries; 10.2 ppb in cherries	75–88%	Lambropoulou and Albanis 2003
Various fruits and vegetables	Homogenization of sample (adding water if needed) and adsorption on activated Florisil to produce a free-flowing powder. Elution with ethyl acetate or methylene chloride.	GC/NPD	4 ppb	91–103% at 0.05 mg/kg	Kadenczki et al. 1992
Various produce	Homogenization of sample and extraction with acetonitrile, filtration, addition of salt and solvent evaporation. Redissolution of residue in acetone for analysis.	GC/FPD or alkali FID	100 ppb	96% (17% RSD)	Hsu et al. 1991
Various prepared foods	Blending of sample with acetone, filtration and transfer to Hydromatrix column. Elution with methylene chloride and concentration.	GC/FPD	No data	91% at 100 ppb	Hopper 1988
Pasta, eggs	Blending of samples with acetone and extraction with dichloromethane and acetone, water removal and volume reduction. Cleanup using carbon-celite (pasta) or C_{18} SPE (eggs).	GC/FPD	~1 ppb	Pasta: 80% at 30 ppb; eggs: 93% at 13 ppb	Leoni et al. 1992
Cow's milk	Extraction of milk 3 times with 70% acetonitrile in water, filtration, removal of fat by zinc acetate addition, and partitioning with methylene chloride. Reduction of volume after drying.	GC/FPD (P-mode)	10 ppb	89% (3.8% RSD) at 100 ppb	Toyoda et al. 1990
Cow's milk	Homogenization of milk, acetonitrile and ethanol followed by equilibration with a mixture of light petroleum-acetonitrile-ethanol and separation of the upper phase and elution through a solid matrix cartridge. Concentration and drying of the eluates to a residue that is dissolved.	GC/FPD	No data (0.003 MDL)	84% at 0.42 µg/mL	Di Muccio et al. 1996

Table 7-2. Analytical Methods for Determining Diazinon and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Lanolin	Dissolution in hexane and extraction with acetonitrile. Addition of 5% NaCl in water to acetonitrile and back-extraction with hexane. Washing of hexane extract with water, volume reduction and fractionation using Florisil.	GC/FPD (526 nm); GC/AED; GC/MS	GC/FPD 0.03 ppm; GC/AED 0.6 ppm (phosphorus monitor); 0.3 ppm (sulfur monitor); GC/MS 0.6 ppm	90% (6.4% RSD) at 1 ppm; 95% (5.6% RSD) at 2 ppm	Miyahara et al. 1992

[a]Unless otherwise stated, diazinon was determined.

AED = atomic emission detection; FPD = flame photometric detector; FPD = flame photometric detector; GC = gas chromatography; HPLC = high performance liquid chromatography; HS = head space, KCl = potassium chloride; K-D = Kuderna-Danish; LSE = liquid-solid extraction, MDL = method detection limit; MS = mass spectrometry; MTBE = methyl tert-butyl ether; NaCl = sodium chloride; NPD = nitrogen phosphorus detector; PUF = polyurethane foam; RSD = relative standard deviation; SFC = supercritical fluid chromatography; SIM = selected ion monitoring; SPE = solid phase extraction; SPME = solid-phase microextraction, TLC = thin layer chromatography; UV = ultraviolet absorbance detection

conjunction with a MS detector, an NPD, or an FPD. Sample preparation methods vary depending on the sample matrix (EPA 1995a, 1995b; Mallet et al. 1990; OSHA 1986). The method of Williams et al. (1987) is applicable to both diazinon and diazoxon. The NIOSH method (NIOSH 1994) has been fully validated for use in occupational settings where regulatory exposure limits are of concern.

Many methods were reported for the determination of diazinon in water. Sample preparation methods include either some form of liquid/liquid extraction or the use of SPE, usually C_{18}-silica, for isolation of diazinon residues. Mallet et al. (1990) reported a method for environmental water based on HPLC/ultra violet (UV) absorbance detection with either direct injection of the water or of an aliquot of an extract. The LODs were as low as 0.5 µg/L with the extraction approach. Mattern et al. (1991) reported a LOD for diazinon in surface water of 0.0005 ppb using GC in conjunction with chemical ionization ion trap MS. Lopez-Avila et al. (1985) reported an isotope dilution GC/MS selected ion monitoring (SIM) method that is applicable to water or soil after solvent extraction. Recoveries were stated to be 89% at 1 ppb in water and 103% at 20 ppb in soil. An LOD of 0.025 µg/kg was reported for diazinon in water with a recovery of 92% (2% RSD) by Seiber et al. (1990). SPE provides an easy method to isolate residues and can greatly reduce the amounts of solvent used in sample preparation. Driss et al. (1993) preconcentrated diazinon from drinking water onto C18-silica or polystyrene-divinylbenzene co-polymer with a subsequent backflush onto an HPLC column (UV detection). LODs as low as 30 µg/L were reported. Kwakman et al. (1992) preconcentrated diazinon from drinking and river water onto C_{18}-SPE disks and eluted the adsorbed compounds directly into a GC pre-column. Detection was by NPD and excellent LODs (20 pg/L) and recoveries (>95% with <4% RSD at 200 pg/L) were reported. Although most of the SPE methods boasted good recoveries and LODs, one reference noted that the pesticide can associate with dissolved organic matter (primarily humic materials) resulting in poor retention by the SPE material (Johnson et al. 1991). This can reduce method recoveries.

Diazinon can be measured in air after pre-concentration from air onto some adsorbent material with subsequent extraction. A method for diazinon in air has been reported that is based on the use of polyurethane foam (PUF) to adsorb the pesticide from the air as the air is pulled through the PUF (Hsu et al. 1988). The PUF is then Soxhlet-extracted and the extract volume reduced prior to capillary GC/MS analysis. An LOD of 55 ng/m^3 (5.5 m^3 sample) and recovery of 73% were reported. Another study was described in which the diazinon levels in indoor air were monitored following periodic application of the pesticide for insect control (Williams et al. 1987). In this method, air is pulled through a commercially available adsorbent tube to concentrate diazinon. The tube is then extracted with acetone prior to GC/NPD analysis. No data were provided for the LOD, but recoveries in excess of 90% were reported at

the 0.1 and 1 μg/m^3 levels. This paper also indicated that diazinon can be converted to diazoxon by ozone and NO_x in the air during the sampling process.

SFE is also used in sample preparation methods. Supercritical trifluoromethane has been shown to extract diazinon from glass beads with a recovery of 86% (Hillmann and Bächmann 1995). Organophosphorus pesticides have also been recovered from Tenax-GC, an adsorbent used to collect diazinon during air sampling, and analyzed directly by GC (Raymer and Velez 1991). Supercritical fluid chromatography (SFC) has also been used for the determination of diazinon in water where 75 μL were injected (Zegers et al. 1994b). Using thermionic detection, the LOD was about 1 μg/L (1 ppb) with a reproducibility of better than 7% at the 5–15 μg/L level. The same authors also published an SFC-based method for cucumber, lettuce, and grapes (Zegers et al. 1994a) but did not specify the LOD and recovery.

Three standardized methods were found in the *Official Methods of Analysis of the Association of Official Analytical Chemists* (AOAC 1990a, 1990b, 1990c). The first of these methods is based on the extraction of crops (kale, endive, carrots, lettuce, apples, potatoes, and strawberries) with ethyl acetate and isolation of the residue followed by a sweep codistillation cleanup prior to GC/thermionic detection (Method 968.24). In the second method (Method 970.52), the sample is extracted with acetonitrile, and the residue is partitioned into petroleum ether followed by Florisil clean-up and GC/potassium chloride (KCl) thermionic detection. Chemical identifications are based on combinations of gas, thin-layer, and paper chromatography. The recovery for diazinon in this method is stated to be greater than 80%; no data on limits of detection were given. The third method utilizes the same extraction and clean-up techniques as the second and then GC/FPD for detection (Method 970.53).

Several methods employ the homogenization of the plant material with aqueous acetonitrile (Hsu et al. 1991; Liao et al. 1991) or other polar organic solvents such as acetone/methanol mixtures (Hong et al. 1993). Phase separation is brought about with the addition of a salt. The acetonitrile approach is preferred by the California Department of Food and Agriculture because of the higher recoveries possible (see Table 7-2) (Lee et al. 1991). The advantage of acetonitrile is found in its ability to more readily solvate residues and in the ease with which the phase separation can be accomplished through the addition of salt (Lee et al. 1991). Reported LODs for diazinon were typically 10–50 ppb. One of the methods eliminated any clean-up steps after the initial extraction (Hsu et al. 1991) to provide a method with a faster turnaround time with some loss in sensitivity (LOD approximately 100 ppb) relative to the purified samples.

Methods found for the determination of diazinon in animal products also used homogenization with a polar organic solvent as the first step in residue recovery. Toyoda et al. (1990) isolated diazinon from cow's milk via partition into methylene chloride after extraction of the milk with 70% acetonitrile in water. Based on GC/FPD, an LOD of 10 ppb and a recovery of 89% (3.8% RSD) at 100 ppb were reported. Diazinon residues in eggs were studied (Leoni et al. 1992) after blending the eggs with acetone and partitioning into dichloromethane and acetone followed by C_{18}-silica SPE. Based on GC/FPD analysis, an LOD of 1 ppb and a recovery of 93% at 13 ppb were reported.

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

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

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Section 3.8.1 reported on biomarkers used to identify or quantify exposure to diazinon. Some methods for the detection of the parent compound in biological samples were described above. The parent chemical is quickly metabolized so the determination of metabolites can also serve as biomarkers of exposure. The use of liquid chromatography (LC) coupled to hybrid quadruple time-of-flight (QTOF) MS has recently been reported for the elucidation and confirmation of diazinon metabolites in biological samples (Ibanez et al. 2006). The most specific biomarkers will be those metabolites related to 2-isopropyl-6-methyl-4-pyrimidine (IMHP). Methods for the detection of this compound in human urine have been reported (Olsson et al. 2003; Yokley et al. 2000). Also a method for IMHP and its oxidized

metabolite, 2-(1'-hydroxy-1'-methyl)-ethyl-6-methyl-4-hydroxypyrimidine, in dog urine has been described by Lawrence and Iverson (1975) with reported sensitivities in the sub-ppm range. Other metabolites most commonly detected are diethylphosphate (DEP) and diethylthiophosphate (DETP), although these compounds are not specific for diazinon as they also arise from other diethylphosphates and phosphorothioates (Drevenkar et al. 1993; Kudzin et al. 1991; Mount 1984; Reid and Watts 1981; Vasilic et al. 1993). Further studies designed to refine the identification of metabolites specific to diazinon and provide dosimetric data will be useful in the search for a more dependable biomarker of diazinon exposure.

Effect. Biomarkers of effect include plasma cholinesterase (ChE) and erythrocyte (RBC) and brain acetylcholinesterase (AChE), enzymes inhibited by insecticidal organophosphorus compounds (see Chapter 3). Rapid, simple, and specific methods should be sought to make assays readily available to the clinician. Currently, no effect specific to diazinon exposure has been identified by any study. Future studies designed to provide such information would be useful in identifying exposure to diazinon.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Human exposure to diazinon occurs via inhalation of ambient air; ingestion of contaminated food and water; and dermal uptake through occupational and non-occupational contact with contaminated soils, surface water, and commercial preparations. Methods have been reported for the measurement of diazinon in various foods, soils, sludges, sediment, solid wastes, waste water, drinking water, and air. The methods of Hsu et al. (1988) (LOD of 55 ng/m^3) Burright (OSHA 1986) (LOD 3.0 μg/m^3) are adequate for the determination of diazinon in air. If a 70-kg individual is assumed, method LODs of 0.007 mg/L (7 ppb) and 0.007 mg/kg (7 ppb) in water and foods, respectively, are required for the method to be adequate at the oral intermediate MRL. All of the methods for detection of diazinon in water shown in Table 7-2 are adequate. With regard to foods, the methods of Kadenczki et al. (1992) and Leoni et al. (1992) for detection of diazinon are adequate. Methods for other non-fatty crops would need to be validated or developed if routine use were desired. Di Muccio et al. (1996) describe a quick and simple method for the determination of diazinon in cow's milk; however, no data were provided given on LODs. Additional methods for detection of diazinon in fatty foods are needed to permit the evaluation of the residues in those fatty media.

There are also methods for the analysis of diazinon degradation products in air, water, and soil. Ibanez et al. (2006) have reported a method for the elucidation and confirmation of degradation products in environmental samples. Williams et al. (1987) published a method for diazinon and its oxon (diazoxon)

in air. Other methods have been reported for diazinon, its oxon, and hydrolysis products in water (Suffet et al. 1967), soils and water (Lichtenstein et al. 1968), and soil (Burkhard and Guth 1979). The hydrolysis product IMHP was studied along with diazoxon in submerged soil (Sethunathan and Yoshida 1969). Suffet et al. (1967) demonstrated the ability of GC to separate diazinon, diazoxon, and IMHP. However, no validated methods for the determination of diazoxon or IMHP were found. Thus, additional methods are needed for the quantitative analysis of diazinon transformation products in environmental matrices. It will also be important to establish MRLs for the transformation products to put the analytical requirements into perspective.

7.3.2 Ongoing Studies

The following information was found as a result of a search of the Federal Research in Progress database (FEDRIP 2006).

Researchers at the University of Puerto Rico, Clemson University, and the University of Tennessee are collaborating in a Multi-State Regional project funded by the U.S. Department of Agriculture to develop environmentally friendly procedures and methods for water sampling of crop management chemicals, including diazinon, which can be used in field situations. Procedures for solid-phase field extraction techniques of water, and stability during storage and shipment of the field water samples to analytical laboratories for testing is being investigated. The study began on October 1, 2003 and is projected to end September 30, 2008. Recent results are to be published in the Journal of Agriculture and Food Science.

8. REGULATIONS AND ADVISORIES

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

ATSDR has derived an intermediate-duration inhalation MRL of 0.01 mg/m^3 for diazinon based on a NOAEL of 1.57 mg/m^3 for inhibition of erythrocyte acetylcholinesterase (RBC AChE) in rabbits (Hartman 1990). The NOAEL of 1.57 mg/m^3 was adjusted from intermittent exposure (4 hours/day, 5 days/week) to a continuous exposure scenario (duration-adjusted NOAEL = 0.28 mg/m^3). A $NOAEL_{HEC}$ (human equivalent concentration) of 0.44 mg diazinon/m^3 was derived from the duration-adjusted NOAEL using EPA (1994b) methodology (see Appendix A for details). The $NOAEL_{HEC}$ of 0.44 mg/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability).

ATSDR has derived an acute-duration oral MRL of 0.006 mg/kg/day for diazinon based on a NOAEL of 0.6 mg/kg/day and a LOAEL of 1.2 mg/kg/day for >20% RBC AChE inhibition in rats (Davies and Holub 1980a). The NOAEL of 0.6 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ATSDR has derived an intermediate-duration oral MRL of 0.002 mg/kg/day for diazinon based on the results of benchmark dose (BMD) analysis of RBC AChE inhibition in female rats exposed to diazinon in the diet (Davies and Holub 1980a). The resulting $BMDL_{20}$ of 0.2238 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). See Appendix A for details regarding BMD analysis.

ATSDR has derived a chronic-duration oral MRL of 0.0007 mg/kg/day for diazinon based on a NOAEL of 0.065 mg/kg/day and a LOAEL of 5.5 mg/kg/day for >20% RBC AChE inhibition in male and female rats (Kirchner et al. 1991). The NOAEL of 0.065 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

EPA (IRIS 2008) does not list an oral reference dose (RfD) or an inhalation reference concentration (RfC) for diazinon.

Table 8-1. Regulations and Guidelines Applicable to Diazinon

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2007
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines	Excluded from guideline value derivation[a]	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)[b,c]	0.01 mg/m^3	ACGIH 2007
EPA	AEGL	No data	EPA 2006a
	Hazardous air pollutant	No data	EPA 2006c 42 USC 7412
NIOSH	REL (10-hour TWA)[d]	0.1 mg/m^3	NIOSH 2005
	IDLH	No data	
OSHA	PEL (8-hour TWA) for general industry	No data	OSHA 2005 29 CFR 1910.1000
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2006b 40 CFR 116.4
	Drinking water standards and health advisories		EPA 2006k
	1-day health advisory for a 10-kg child	0.02 mg/L	
	10-day health advisory for a 10-kg child	0.02 mg/L	
	DWEL	0.007 mg/L	
	Lifetime	0.001 mg/L	
	National primary drinking water standards; monitoring requirements for unregulated contaminants		EPA 2006d 40 CFR 141.40
	Minimum reporting level	0.5 µg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	1 pound	EPA 2006f 40 CFR 117.3
	Water quality criteria for non-priority pollutants		EPA 2006e
	Freshwater		
	CMC and CCC	0.17 µg/L	
	Saltwater		

Table 8-1. Regulations and Guidelines Applicable to Diazinon

Agency	Description	Information	Reference
	CMC and CCC	0.82 µg/L	
NATIONAL *(cont.)*			
DOT	Marine pollutant	Yes	DOT 2005 49 CFR 172.101, Appendix B
c. Food			
FDA	Bottled drinking water	No data	FDA 2005a
EPA	Tolerances for residues (see 40 CFR 180.153 for a complete listing of tolerances for residues on raw agricultural commodities)	Range: 0.1–40 ppm	EPA 2006i 40 CFR 180.153
USDA	Domestic quarantine notices; authorized insecticide	Fire ants and containerized nonbearing blueberries and fruit and nut plants	USDA 2006 7 CFR 301.81-10
d. Other			
ACGIH	Carcinogenicity classification	A4[e]	ACGIH 2007
	Biological exposure indices (for acetylcholinesterase inhibiting pesticides)		
	Cholinesterase activity in red blood cells (sampling time is discretionary)	70% of individual's baseline	
EPA	Carcinogenicity classification	Group E[f]	EPA 2006k
	RfC	No data	IRIS 2008
	RfD	No data	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	Yes	EPA 2006g 40 CFR 302.4
	Reportable quantity	1 pound	
	Effective date of toxic chemical release reporting	01/01/95	EPA 2006h 40 CFR 372.65

Table 8-1. Regulations and Guidelines Applicable to Diazinon

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NTP	Carcinogenicity classification	No data	NTP 2004

[a]Excluded from guideline value derivation because it is unlikely to occur in drinking water.
[b]Inhalable fraction and vapor
[c]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors, liquids, or solids.
[d]Skin designation: indicates the potential for dermal absorption; skin exposure should be prevented as necessary through the use of good work practices, gloves, coveralls, goggles, and other appropriate equipment.
[e]A4: not classifiable as a human carcinogen
[f]Group E: evidence of noncarcinogenicity for humans

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Exposure Guideline Level; CCC = Criterion Continuous Concentration; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; CMC = Criteria Maximum Concentration; DOT = Department of Transportation; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FR = Federal Register; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; USDA = United States Department of Agriculture; WHO = World Health Organization

The International Agency for Research on Cancer (IARC) and the National Toxicology Program (NTP) have not classified diazinon for human carcinogenicity (IARC 2007; NTP 2004). The 2006 edition of the EPA Drinking Water Standards and Health Advisories includes a Group E (evidence of noncarcinogenicity for humans) designation for diazinon (EPA 2006k). The American Conference of Governmental Industrial Hygienists (ACGIH) has assigned diazinon to carcinogenicity category A4 (not classifiable as a human carcinogen) (ACGIH 2007).

OSHA has not required employers of workers who are occupationally exposed to diazinon to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs) (OSHA 2005). The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended an 8-hour Threshold Limit Value-Time-Weighted Average (TLV-TWA) of 0.01 mg/m^3 for diazinon (ACGIH 2007). NIOSH has recommended a 10-hour (TWA) Recommended Exposure Limit (REL) of 0.1 mg/m^3 for diazinon (NIOSH 2005).

EPA regulates diazinon under the Clean Water Act (CWA) and the Clean Air Act (CAA) and has designated it as a hazardous substance and a hazardous air pollutant (HAP) (EPA 2006b, 2006c). Diazinon is on the list of chemicals appearing in “Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" (EPA 2006h). Diazinon has been assigned a reportable quantity (RQ) limit of 1 pound (EPA 2006g). The RQ represents the amount of a designated hazardous substance which, when released to the environment, must be reported to the appropriate authority.

EPA recommends a criterion continuous concentration (CCC) and a criteria maximum concentration (CMC) of 0.17 μg/L for fresh water and 0.82 μg/L for salt water (EPA 2006e). The CCC is an estimate of the highest concentration of diazinon in freshwater/saltwater to which aquatic organisms can be exposed indefinitely without resulting in an unacceptable effect; the CMC is the highest concentration in freshwater/saltwater to which aquatic organisms can be exposed for a brief period without resulting in an unacceptable effect.

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), tolerances for residues on raw agricultural commodities for diazinon range from 0.1 to 40 ppm (EPA 2006i); see 40 CFR 180.153 for a complete listing of tolerances for residues and the corresponding raw agricultural commodities.

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10. GLOSSARY

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

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

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

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

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

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

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

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

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

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

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

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

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

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

Immunological Effects—Functional changes in the immune response.

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

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

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

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

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

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

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

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

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

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

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

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

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

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

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

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

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

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

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

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

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

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

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

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

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

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

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a

variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

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

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

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

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

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

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

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

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

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

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

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

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

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

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

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

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

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

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

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

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

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

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

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

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Diazinon
CAS Numbers: 333-41-5
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 5
Species: Rat

Minimal Risk Level: 0.01 [ ] mg/kg/day [X] mg/m^3

Reference: Hartman HR. 1990. 21-Day repeated exposure inhalation toxicity in the rat. EPA guidelines no. 82-4. Laboratory study number 891205. Ciba-Geigy Corporation. Submitted to the U.S. Environmental Protection Agency. MRID41557402.

Experimental design: Four groups of albino rats (10/sex) were exposed (nose only) to aerosols of diazinon (in ethanol) at concentrations of 0, 0.05, 0.46, 1.57, or 11.6 mg/m^3 for 6 hours/day, 5 days/week for 3 weeks. Particle size analysis was performed to ensure that the test aerosols were in the respirable range for the rat. Two control groups were used, one exposed to humidified filtered air only and the other to the carrier vehicle ethanol. The test substance was the liquid MG-8 formulation (88% diazinon). Exposure levels were monitored by gas chromatography. Clinical examinations included ophthalmology, body weight, food consumption, hematology, and blood chemistry (including plasma ChE and RBC AChE activity). At necropsy, organ weights and brain AChE activity were assessed and histopathological examinations were performed on nasal tissues and lungs from all groups and on the spleen, heart, liver, kidney, adrenal gland, and any tissue with gross lesions from the control and 11.6 mg/m^3 groups.

Effect noted in study and corresponding doses: No deaths or changes in body weights or food consumption were observed. Piloerection was noted in most animals, particularly during the first week of exposure, the incidence gradually declining during weeks 2 and 3 of exposure. This sign was neither exposure- nor dose-related and no clinical signs of organophosphate toxicity were observed. No exposure-related ophthalmoscopic or histopathological lesions were found. There were no statistically significant exposure-related effects on hematological parameters, although minimally lower values for erythrocyte count, hemoglobin, and packed red cell volume were observed in female rats of the highest exposure level. A significantly higher lung-to-body weight ratio was observed in female rats of the 0.46 and 1.57 mg/m^3 exposure levels, but not at the highest exposure level. The toxicological significance of this effect is uncertain because no histopathological evidence of exposure-related lung lesions was found. As shown in Table A-1, significant reductions in plasma ChE (marker for exposure) were seen in males at exposure levels $\geq$1.57 mg/m^3 and females at exposure levels $\geq$0.46 mg/m^3. Organophosphate-induced plasma ChE inhibition is typically observed at exposure levels lower than those inducing measurable RBC or brain AChE inhibition. Plasma ChE inhibition is used as an indicator of exposure, but does not serve as a reliable indicator of a neurotoxic effect. Therefore, plasma ChE inhibition was not considered relevant to the selection of the critical effect for diazinon. However, inhibition of RBC AChE and brain AChE represents a relevant neurological effect. In the principal study (Hartman 1990), significant reductions in RBC AChE activity (surrogate marker for neural AChE activity) were seen in male rats at 11.6 mg/m^3 and in female rats at 1.57 and 11.6 mg/m^3 (Table A-1). Treatment-related 20–59% RBC or brain AChE inhibition is considered to represent a less serious adverse effect in the absence of more clear indicators of neurotoxicity (Chou and Williams-Johnson 1998). The 10% RBC AChE inhibition observed in the 1.57 mg/m^3 group of female rats is below the level of inhibition considered to represent an adverse effect. Therefore, the 1.57 mg/m^3 exposure level is a

NOAEL and the highest exposure level (11.6 mg/m^3) is the lowest-observed-adverse-effect level (LOAEL) for 36 and 39% RBC AChE inhibition in the male and female rats, respectively. There was no significant difference between brain AChE activity in any of the exposure groups of male rats and that of vehicle controls. All diazinon-exposed groups of female rats exhibited significantly decreased brain AChE activity, relative to vehicle controls. The report of significantly increased brain AChE inhibition in the female rats of all exposure levels is indicative of an inherent problem with the brain data set, perhaps related to tissue collection or quantitative analysis of enzymatic activity in the brain tissue of the female rats. Furthermore, results of repeated oral dosing (Singh 1988) indicate that the male and female rats are comparably sensitive to diazinon-induced effects on both RBC and brain AChE activity. Therefore, the report (Hartman 1990) of significant brain AChE inhibition in the female rats exposed to diazinon by inhalation at levels much lower than the LOAEL of 11.6 mg/m^3 for RBC AChE inhibition is questionable and a clear LOAEL for brain AChE inhibition cannot be determined.

Table A-1. Relative Change (Percent of Control Values) in Cholinesterase Activities in Male and Female Rats Following Exposure to Aerosols of Diazinon for 90 Days

	Plasma ChE	RBC AChE	Brain AChE
Male rats			
0.05 mg/m^3	+9%[a]	+2%	-1%
0.46 mg/m^3	-5%	-5%	+1%
1.57 mg/m^3	-14%[b]	-6%	-4%
11.6 mg/m^3	-19%[b]	-36%[a]	-3%
Female rats			
0.05 mg/m^3	-3%	-1%	-24%[a]
0.46 mg/m^3	-20%[b]	+6%	-17%[b]
1.57 mg/m^3	-27%[a]	-10%[b]	-20%[b]
11.6 mg/m^3	-43%[a]	-39%[a]	-37%[a]

[a]statistically significantly different from control (p≤0.01)
[b]statistically significantly different from control (p≤0.05)

AChE = acetylcholinesterase; ChE = cholinesterase; RBC = red blood cell

Source: Hartman 1990

Dose and end point used for MRL derivation: A NOAEL of 1.57 mg/m^3; the LOAEL was 11.6 mg/m^3 for 36–39% RBC AChE inhibition in male and female rats of the principal study

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [X] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The NOAEL of 1.57 mg/m^3 was adjusted for intermittent exposure as follows:

$NOAEL_{ADJ}$ = 1.57 mg diazinon/m^3 x 6 hours/24 hours x 5 days/7 days = 0.28 mg diazinon/m^3

A regional deposited dose ratio ($RDDR_{ER}$) of 1.558 for extrarespiratory effects was used to extrapolate from rats to humans. The $RDDR_{ER}$ was calculated using EPA's software (Version 2.3) (EPA 1994b) for calculating RDDRs and the parameters listed in Table A-2.

Table A-2. Parameters[a] Used to Calculate the Regional Deposited Dose Ratio ($RDDR_{ER}$) for Diazinon-induced Extrarespiratory Effects Using EPA's Software (Version 2.3)

Biological parameters[b]	Rat	Human
Surface area		
Extrathoracic	15 cm^2	200 cm^2
Tracheobronchial	22.5 cm^2	3,200 cm^2
Pulmonary	0.34 m^2	54 m^2
Minute ventilation	147.24 mL	13.8 L
Body weight	196 g	70 kg

[a]Mass Median Aerodynamic Diameter (MMAD) = 0.85 µm from lower limit of 0.8 µm and upper limit of 0.9 µm for the 1.57 mg/m^3 exposure group of female rats reported by Hartman (1990); Geometric Standard Deviation (GSD) = 1.3 µm from lower limit of 1.2 µm and upper limit of 1.4 µm reported by Hartman (1990).
[b]Parameters are default values for rats and humans from the EPA software, except for the rat body weight which was the mean body weight for the 1.57 mg/m^3 exposure group of female rats.

Source: Hartman 1990

The human equivalent concentration was calculated using Equation 4-5 (EPA 1994b) as follows:

$NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x $RDDR_{ER}$ = 0.28 mg diazinon/m^3 x 1.558 = 0.44 mg diazinon/m^3

The $NOAEL_{HEC}$ of 0.44 mg/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability), resulting in an intermediate-duration inhalation MRL of 0.01 mg/m^3.

Was a conversion used from intermittent to continuous exposure? Yes.

Other additional studies or pertinent information that lend support to this MRL: This is the only available well-conducted, intermediate-duration inhalation study for diazinon. In an acute-duration study in which rats were exposed to 2,300 mg/m^3 diazinon for 4 hours (Holbert 1989), mild signs of organophosphate toxicity were noted (nasal discharge, salivation).

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.; Carolyn Harper, Ph.D.; Paula Burgess, M.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Diazinon
CAS Numbers: 333-41-5
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 23
Species: Rat

Minimal Risk Level: 0.006 [X] mg/kg/day [ ] mg/m^3

Reference: Davies DB, Holub BJ. 1980a. Toxicological evaluation of dietary diazinon in the rat. Arch Environ Contam Toxicol 9(6):637-650.

Experimental design: Groups of female Wistar rats (50/group) were exposed to diazinon (99.2% purity) in the diet at concentrations of 0, 5, 10, or 15 ppm for 92 days. Interim assessments of neurological end points included treatment day 12 assessment, which represents acute-duration oral exposure. Blood samples were collected on treatment days 3, 8, and 12 from 10 rats/group for assessment of plasma ChE and RBC AChE activity. Other groups of similarly-treated rats were sacrificed (n=6) for assessment of brain AChE activity. All rats were assessed daily for clinical signs of neurotoxicity and body weights and food intake were monitored throughout the treatment period. The study authors reported starting mean body weight (0.139 kg), mean body weight gain (0.00163 kg/day), and mean food consumption (0.0178 kg/day) for all rats, and indicated that they did not significantly differ among treatment groups. Using the average body weight gain for 12 days (0.00163 kg/day x 12 days=0.02 kg), the average body weight for the 12-day period was equal to the starting body weight (0.139 kg) plus one-half the body weight gain during the 12-day period (0.5x0.02 kg)=0.149 kg. The diazinon dose equals the product of the diazinon concentration in food times the mean daily food consumption divided by the average body weight. Calculated in this manner, the doses to the 5-, 10-, and 15-ppm exposure groups were 0.6, 1.2, and 1.8 mg/kg/day, respectively.

Effect noted in study and corresponding doses: No clinical signs of toxicity were observed in any of the treated groups. Compared to controls, significant plasma ChE inhibition was observed in all diazinon-treated groups at all timepoints (including treatment days 3, 8, and 12). At treatment day 12, treatment-related effects included 43, 70, and 73% plasma ChE inhibition and 5, 22, and 33% RBC AChE inhibition in the 0.6, 1.2, and 1.8 mg/kg/day dose groups, respectively. There was no significant effect on brain AChE activity. Plasma ChE inhibition is used as an indicator of exposure, but does not serve as a reliable indicator of a neurotoxic effect. Therefore, plasma ChE inhibition was not considered relevant to the selection of the critical effect for diazinon. However, inhibition of RBC AChE and brain AChE represents a relevant neurological effect. Treatment-related 20–59% RBC or brain AChE inhibition is considered to represent a less serious adverse effect in the absence of more clear indicators of neurotoxicity. The principal study (Davies and Holub 1980a) identified a NOAEL of 0.6 mg/kg/day and a LOAEL of 1.2 mg/kg/day for 22% RBC AChE inhibition at interim day 12 assessment of female rats administered diazinon in the diet for 92 days.

Dose and end point used for MRL derivation: A NOAEL of 0.6 mg/kg/day; the LOAEL was 1.2 mg/kg/day for 22% RBC AChE inhibition

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses were calculated from reported mean values for initial body weight, food consumption, and body weight gain for the first 12 days of treatment.

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

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

Other additional studies or pertinent information that lend support to this MRL: In an unpublished study (EPA 1996), male and female rats were administered diazinon in the diet for 28 days and assessed for cholinesterase inhibition at weeks 1, 2, and 4. A dose of 2.4 mg/kg/day resulted in 38–59% RBC AChE inhibition in both males and females, which was observed as early as week 1 and peaked at week 2. The next lower dose (0.02 mg/kg/day) represented a NOAEL. The principal study for deriving the acute-duration oral MRL for diazinon (Davies and Holub 1980a) was performed using only female rats. However, Davies and Holub (1980a) noted that dietary studies in their laboratory had demonstrated that female rats were more sensitive than male rats to diazinon induced plasma ChE and RBC and brain AChE inhibition. In light of this finding, the selection of RBC AChE inhibition in the female rats as the critical effect from the principal study that assessed the critical effect only in female rats (Davies and Holub 1980a) is appropriate.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.; Carolyn Harper, Ph.D.; Paula Burgess, M.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Diazinon
CAS number(s): 333-41-5
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 63
Species: Rat

Minimal Risk Level: 0.002 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Davies DB, Holub BJ. 1980a. Toxicological evaluation of dietary diazinon in the rat. Arch Environ Contam Toxicol 9(6):637-650.

Note: Available intermediate-duration oral (dietary) toxicity studies of diazinon include 10 studies in rats and 2 studies in dogs (see Table A-4, page A-14, for a summary of NOAELs and LOAELs for RBC and brain AChE inhibition identified in these studies). Although dose spacing is variable, and in some studies may be in excess of 100-fold for levels at or below identified LOAELs for AChE inhibition, these studies collectively indicate that the threshold for less serious AChE inhibition occurs in rats and dogs at repeated oral dose levels between 0.2 and 2 mg/kg/day. The report of Davies and Holub (1980a) includes results from separate 35-, 42-, and 92-day studies.

Experimental design: In the principal study, groups of female Wistar rats (16/group) were exposed to diazinon (99.2% purity) in the diet at concentrations of 0, 1, 2, 3, or 4 ppm for 42 days (Davies and Holub 1980a). Blood samples were collected periodically from 10 rats/group for assessment of plasma ChE and RBC AChE activity. Six rats per group were sacrificed on day 35 for assessment of brain AChE activity. All rats were assessed daily for clinical signs of neurotoxicity and body weights and food intake were monitored throughout the treatment period. The study authors stated that female rats were used in the study because they were noted to be more sensitive than male rats to the neurotoxic effects of diazinon. The study authors reported starting mean body weight (0.149 kg), mean body weight gain (0.00259 kg/day), and mean food consumption (0.0178 kg/day) for all rats, and indicated that they did not significantly differ among treatment groups. Using the average body weight gain for 42 days (0.00259 kg/day x 42 days=0.11 kg), the average body weight for the 42-day period was equal to the starting body weight (0.149 kg) plus one-half the body weight gain during the 42-day period (0.5x0.11 kg)=0.2 kg. The diazinon dose equals the product of the diazinon concentration in food times the mean daily food consumption divided by the average body weight. Calculated in this manner, the doses to the 1-, 2-, 3-, and 4-ppm exposure groups were 0.09, 0.18, 0.27, and 0.36 mg/kg/day.

Effects noted in study and corresponding doses: No clinical signs of toxicity were observed in any of the treated groups (Davies and Holub 1980a). Significant plasma ChE inhibition was observed at most timepoints in all diazinon-treated groups, relative to controls. The magnitude of inhibition in all treatment groups increased with time and appeared to peak around day 35, remaining near the peak level for the remaining 7 treatment days. Maximum plasma ChE inhibition in the 1, 2, 3, and 4 ppm treatment groups was approximately 35, 50, 55, and >60%, respectively. Plasma ChE inhibition is used as an indicator of exposure, but does not serve as a reliable indicator of a neurotoxic effect. Therefore, plasma ChE inhibition was not considered relevant to the selection of the critical effect for diazinon. Through treatment day 35, there was no significant treatment-related effect on RBC AChE activity in any of the treatment groups. However, on treatment day 42, significant RBC AChE inhibition was observed at

treatment levels of 2, 3, and 4 ppm (magnitude 9, 20, and 22%, respectively). There were no indications of treatment-related significant brain AChE inhibition at any timepoint during the 42 days of treatment. The results of RBC AChE activity in the female rats of the principal study (Davies and Holub 1980a) are presented in Table A-3. Inhibition of RBC AChE and brain AChE represents a relevant neurological effect. Treatment-related 20–59% RBC or brain AChE inhibition is considered to represent a less serious adverse effect in the absence of more clear indicators of neurotoxicity. The principal study (Davies and Holub 1980a) identified a NOAEL of 0.18 mg/kg/day and a LOAEL of 0.27 mg/kg/day for 20% RBC AChE inhibition in female rats administered diazinon in the diet for 42 days.

Table A-3. RBC AChE Data From Female Rats Exposed to Diazinon in the Diet for 42 Days

Dose group (mg/kg/day)	Number of rats	RBC AChE activity (µmole/mL packed cells/minute)	Percent RBC AChE inhibition
0	10	0.74±0.05[a]	
0.09	10	0.68±0.07	8
0.18	10	0.67±0.06	9
0.27	10	0.59±0.04	20
0.36	10	0.58±0.02	22

[a]Mean±standard error

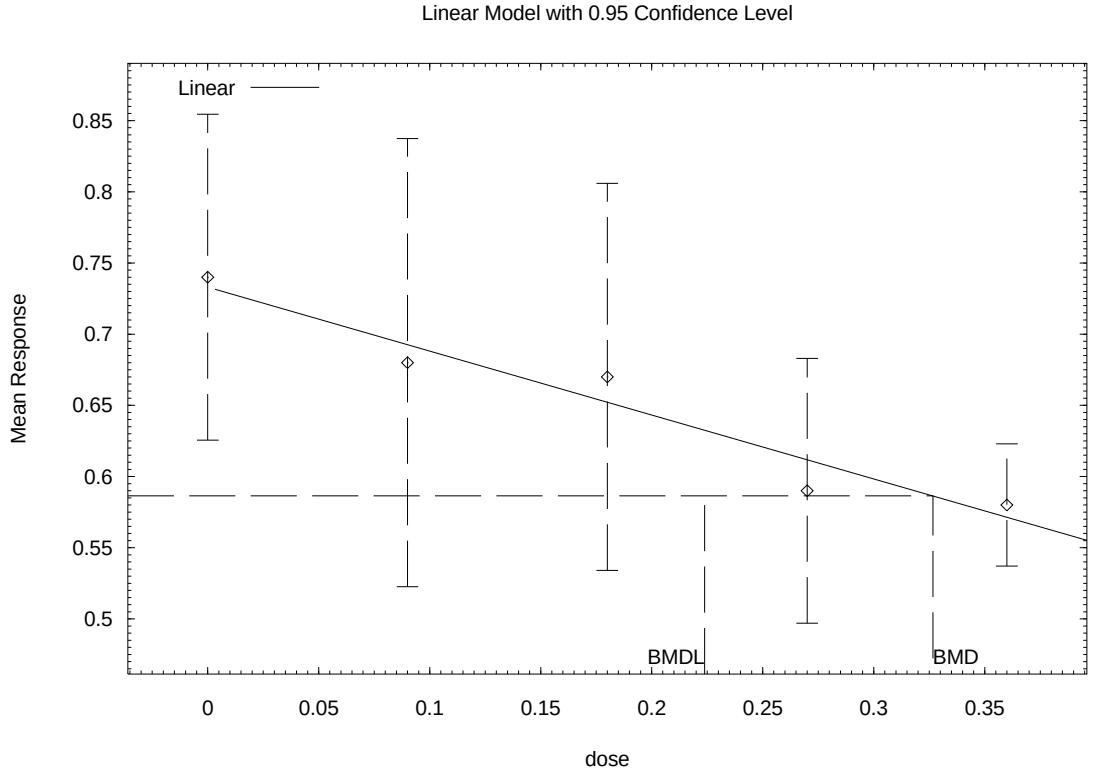
AChE = acetylcholinesterase; RBC = red blood cell

Source: Davies and Holub 1980a

The linear model in the EPA Benchmark Dose Software (Version 1.3.2) was fit to the female rat data for RBC AChE activity shown in Table A-3. A benchmark response (BMR) of 20% below the control mean RBC AChE activity was selected because treatment-related 20–59% RBC or brain AChE inhibition is considered to represent a less serious adverse effect in the absence of more clear indicators of neurotoxicity (Chou and Williams-Johnson 1998). Although the linear model provided adequate fit to the data from Table A-3, as indicated by acceptable p values for tests for (1) differences in response and/or variances among dose levels, (2) homogeneous or non-homogeneous variance, and (3) model mean fit, a non-homogeneous variance model run was suggested. Adequate fit was also provided by the linear model using non-homogeneous variance, which resulted in a BMD_{20} of 0.3267 mg/kg/day and a $BMDL_{20}$ of 0.2238 mg/kg/day. Because the simplest model, the linear model, provided adequate fit to the RBC AChE data from the 42-day rat study of Davies and Holub (1980a), the application of more complex continuous variable models was not considered necessary. The $BMDL_{20}$ of 0.2238 mg/kg/day served as the point of departure for deriving an intermediate-duration oral MRL for diazinon.

Figure A-1 is a plot of predicted and observed levels of RBC AChE activity in the female dogs of the principal study (Davies and Holub 1980a) generated from the linear model using non-homogeneous variance.

Figure A-1. Predicted and Observed Levels of RBC AChE Activity in Female Dogs Orally Exposed to Diazinon for 42 Days*



*BMD and BMDL (in mg/kg/day) are associated with a benchmark response of 20% reduction in RBC AChE activity from the control value

The linear model form and parameters output from benchmark dose analysis of RBC AChE activity in the female rats of the principal study (Davies and Holub 1980a) follows:

```
The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

   Dependent variable = MEAN
   Independent variable = dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = alpha*mean(i)^rho

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
```

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Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	0.02612
rho =	0
beta_0 =	0.734
beta_1 =	-0.455556

Variable	Parameter Estimates Estimate	95.0% Wald ConfidenceInterval Std. Err.	Lower Conf. Limit	Upper Conf. Limit
alpha	0.729698	0.927763	-1.08868	2.54808
rho	8.31	2.91288	2.60086	14.0191
beta_0	0.73306	0.0466142	0.641698	0.824422
beta_1	-0.448823	0.162678	-0.767667	-0.129979

Asymptotic Correlation Matrix of Parameter Estimates

	alpha	rho	beta_0	beta_1
alpha	1	0.99	-0.049	0.064
rho	0.99	1	-0.053	0.068
beta_0	-0.049	-0.053	1	-0.93
beta_1	0.064	0.068	-0.93	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev	Chi^2 Res.
0	10	0.74	0.16	0.733	0.235	0.0934
0.09	10	0.68	0.22	0.693	0.186	-0.216
0.18	10	0.67	0.19	0.652	0.145	0.387
0.27	10	0.59	0.13	0.612	0.111	-0.623
0.36	10	0.58	0.06	0.571	0.0835	0.322

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)

APPENDIX A

Var{e(ij)} = alpha*(Mu(i))^rho

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	68.760362	6	-125.520725
A2	76.244732	10	-132.489465
A3	74.537476	7	-135.074952
fitted	72.450460	4	-136.900920
R	64.715236	2	-125.430471

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	23.059	8	0.003289
Test 2	14.9687	4	0.004766
Test 3	3.41451	3	0.332
Test 4	4.17403	3	0.2433

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels. It seems appropriate to model the data

The p-value for Test 2 is less than .05. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .05. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .05. The model chosen seems to adequately describe the data

```
 Benchmark Dose Computation
Specified effect =           0.2

Risk Type        =     Relative risk

Confidence level =          0.95

             BMD =      0.326659

            BMDL =        0.2238
```

The $BMDL_{20}$ of 0.2238 mg/kg/day was divided by a total uncertainty factor (UF) of 100 (10 for extrapolation from animals to humans and 10 for human variability) as follows:

Intermediate-duration oral MRL = $BMDL_{20}$ ÷ UF = 0.2238 mg/kg/day ÷ 100 = 0.002 mg/kg/day

Dose end point used for MRL derivation: $BMDL_{20}$ of 0.2238 mg/kg/day for RBC AChE activity

[ ] NOAEL [ ] LOAEL [X] Benchmark

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses were calculated from reported mean values for initial body weight, food consumption, and body weight gain for the 42-day treatment period.

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

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

Other additional studies or pertinent information that lend support to this MRL: The selection of the BMD_{20} of 0.3267 mg/kg/day and its lower 95% confidence limit ($BMDL_{20}$) of 0.2238 mg/kg/day from the female rats of the principal study (Davies and Holub 1980a) as a point of departure for deriving an intermediate-duration oral MRL for diazinon is supported by the results of several studies (see Table A-4). These studies collectively indicate that the threshold for less serious AChE inhibition occurs in rats and dogs at repeated oral dose levels between 0.2 and 2 mg/kg/day. The derived intermediate-duration oral MRL of 0.002 mg/kg/day is supported by the free-standing NOAEL of 0.03 mg/kg/day identified in four male volunteers administered diazinon in gelatin capsules at a dose level of 0.03 mg/kg/day for 28–31 days.

Table A-4. NOAELs and LOAELs for RBC and Brain AChE Inhibition Following Intermediate-duration Dietary Exposure to Diazinon

Study type estimated doses (mg/kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day) AChE inhibition	Reference
28-Day rat study	0.02 (M, F)	2.4; M, F: 38–59% RBC	EPA 1996
M, F: 0, 0.02, 2.4, 23, 213			
30-Day rat study	ND	2.86; 58% RBC	Davies and Holub 1980b
F: 0, 2.86			
35-Day rat study	0.2	ND	Davies and Holub 1980a
F: 0, 0.009, 0.05, 0.09, 0.2			
42-Day rat study	0.2	0.3; 20% RBC	Davies and Holub 1980a
F: 0, 0.09, 0.18, 0.27, 0.36			
6-Week rat study	0.2 (M, F)	2.0; M, F: 46–61% RBC	EPA 2000a
0, 0.02, 0.05, 0.2, 2, 9.5, 28			
6-Week rat study			EPA 2000a
M: 0, 0.02, 0.04, 0.17, 1.68, 8.6, 25.8	0.17 (M)	1.68; M: 29–35% RBC	
F: 0, 0.02, 0.05, 0.19, 1.82, 9.27, 29	0.19 (F)	1.82; F: 16–35% RBC	
6-Week rat study	0.2 (M, F)	8.4; M: 21% RBC	Singh 1988
M: 0, 0.04, 0.2, 8.4, 165			
F: 0, 0.05, 0.2, 9.4, 198		9.4; F: 21% RBC and 24% brain	
90-Day rat study			Singh 1988
M: 0, 0.03, 0.3, 15, 168	0.3 (M)	15; M: 27% RBC	
F: 0, 0.04, 0.4, 19, 212	0.4 (F)	19; F: 41% RBC	
90-Day rat study	0.018 (M, F)	1.8; M, F: 37–75% RBC	EPA 1996
0, 0.018, 1.8, 18, 180			
92-Day rat study	0.4	0.7; 40% RBC	Davies and Holub 1980a
F: 0, 0.4, 0.7, 1			
4-Week dog study			Barnes 1988
M: 0, 0.02, 0.073, 0.8, 14.68	0.8 (M)	14.68; M: 25% RBC; 31% brain	
F: 0, 0.023, 0.082, 0.75, 15.99	0.75 (F)	5.6; F: 31% RBC; 30% brain	
13-Week dog study	0.02 (M, F)		Barnes 1988
M: 0, 0.0034, 0.02, 5.9, 10.9		5.9; M: 26% RBC; 31% brain	
F: 0, 0.0037, 0.02, 5.6, 11.6		5.6; F: 31% RBC ; 30% brain	

AChE = acetylcholinesterase; F = female; LOAEL = lowest-observed-adverse-effect level; M = male; ND = not determined; NOAEL = no-observed-adverse-effect level; RBC = red blood cell

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.; Carolyn Harper, Ph.D.; Paula Burgess, M.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Diazinon
CAS Numbers: 333-41-5
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 91
Species: Rat

Minimal Risk Level: 0.0007 [X] mg/kg/day [ ] mg/m^3

Reference: Kirchner FR, McCormick GC, Arthur AT. 1991. One/two year oral toxicity study in rats. Ciba-Geigy Corporation. Submitted to the U.S. Environmental Protection Agency. MRID41942002.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Diazinon MG-8 (purity 87.7%) was dissolved in acetone vehicle and added to the diet of male and female Sprague-Dawley rats at concentrations of 0, 0.1, 1.5, 125, or 250 ppm for up to 98 weeks. The study included both untreated and vehicle control groups. According to the study report, the corresponding doses were 0, 0.004, 0.06, 5, and 10 mg/kg/day for males and 0, 0.005, 0.07, 6, and 12 mg/kg/day for females). Averaged among male and female rats, the corresponding doses were 0, 0.0045, 0.065, 5.5, and 11 mg/kg/day. Twenty rats/sex/group were treated for the full 98 weeks. Ten rats/sex/group were treated for 52 weeks and sacrificed for interim assessment. Additional groups of 10 rats/sex were assigned to the untreated control, vehicle control, and 250 ppm groups and assessed for recovery 45 days following 52 weeks of treatment. Animals were observed daily for clinical signs of toxicity. Food consumption, water intake, and body weights were monitored. Ophthalmoscopic examinations were performed during weeks 2, 51, and 97 or 98. Blood was collected at several timepoints between days 88 and 684. Ten animals/sex/group from the 98-week treatment groups received clinical chemistry evaluation at treatment days 88, 181, 356, 390, 552, and 684. Urinalysis was performed on all surviving rats of the 98-week treatment groups at treatment days 81, 189, 350, 545, and 679. All rats were subjected to comprehensive gross and microscopic pathologic examination at death or sacrifice.

Effect noted in study and corresponding doses: There were no apparent treatment-related effects on survival, food or water consumption, body weights, or hematological or urinalysis parameters examined. Due to mortality in all groups including controls the study was terminated at 97 weeks. Ophthalmoscopic and gross and microscopic examinations did not reveal evidence of dose-related effects. The major findings of this study were those of dose-related decreased plasma ChE and RBC and brain AChE activity in both male and female rats. Significantly decreased plasma ChE activity (28–51% lower than controls) was noted in 0.065 mg/kg/day male rats at treatment days 88 and 684, but not at treatment days 181, 356, or 552 and in 0.065 mg/kg/day female rats (approximately 50% lower than controls) at most timepoints. High-dose male and female rats consistently exhibited significantly decreased plasma ChE activity, ranging from 80 to 97% lower than controls. In 0.065 mg/kg/day groups, RBC and brain AChE activity was not significantly decreased at any timepoint. The 5.5 mg/kg/day groups exhibited significantly decreased RBC AChE activity at all timepoints, ranging in magnitude from 15 to 28% and from 22 to 25% in males and females, respectively. At the 5.5 and 11 mg/kg/day levels, the magnitude of the effect did not appear to increase with either duration of treatment or increased dose. Following 52 weeks of treatment and 45 days of recovery, RBC AChE activity had returned to control levels in high-dose male rats and to within 7% of control levels in high-dose female rats. Brain AChE activity was significantly decreased in 5.5 and 11 mg/kg/day male and female rats. In 5.5 and 11 mg/kg/day males, the magnitude

of the effect was effect was 24 and 42%, respectively, after 684 days of treatment, but not significantly different from controls at 370 days. In 5.5 and 11 mg/kg/day female rats, the effect was noted at both 370- and 684-day timepoints; the magnitude of the effect was >24% at 5.5 mg/kg/day and >40% at 11 mg/kg/day. This study identified a NOAEL of 0.065 mg/kg/day (1.5 ppm of diazinon in the diet) and a LOAEL of 5.5 mg/kg/day (125 ppm of diazinon in the diet) for 22–28% decreased RBC AChE activity in male and female rats administered diazinon in the diet for up to 97 weeks, which is considered the critical effect. The effect was observed as early as day 88 of treatment and did not appear to increase in magnitude with duration of treatment.

Dose and end point used for MRL derivation: A NOAEL of 0.065 mg/kg/day; the LOAEL was 5.5 mg/kg/day for 22–28% decreased RBC AChE activity

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Estimated doses were included in the original study.

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

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

Other additional studies or pertinent information that lend support to this MRL: Groups of 5-month-old male and female Beagle dogs (4/sex/group) were administered diazinon MG-8 (87.7% purity) in the diet for 52 weeks at concentrations of 0, 0.1, 0.5, 150, or 300 ppm (Rudzki et al. 1991). The highest dose level was reduced to 225 ppm after 14 weeks due to the lack of body weight gain at the 300 ppm level. According to the study authors, the corresponding diazinon doses (adjusted for purity) were 0, 0.0032, 0.015, 4.7, and 7.7 mg/kg/day for the males and 0, 0.0037, 0.02, 4.5, and 9.1 mg/kg/day for the females. Averaged among male and female dogs, the corresponding doses were 0, 0.0034, 0.017, 4.6, and 7.9 mg/kg/day. Animals were observed daily for clinical signs of toxicity. Food consumption and body weights were monitored throughout the study. Physical, auditory, and ophthalmoscopic examinations were periodically performed. Blood and urine were collected 4 weeks prior to dosing and during treatment weeks 13, 26, 39, and 52 for hematological and clinical chemistry assessment and urinalysis. At death or scheduled sacrifice, organ weights were recorded and all animals were subjected to histological examination of all major organs and tissues. One high-dose male was sacrificed on test day 2 and one female in the 0.5 ppm group was found dead on test day 12. Both deaths were attributed to gastrointestinal infections and the animals were replaced. Clinical signs of toxicity were limited to a single high-dose male that exhibited signs of dehydration and emaciation. Although food consumption in all treatment groups of male and female dogs was lower than that of controls at most timepoints during the 52 weeks of treatment, there was no clear pattern of dose-related decreased food consumption. The 4.6 mg/kg/day dose level may represent a LOAEL for body weight gain in the males, but a clear effect level for body weight gain was not identified in females. Plasma ChE inhibition generally exceeded 20% in all dose groups of males and females, with the exception of the 0.0034 mg/kg/day groups. Significant RBC AChE inhibition (magnitude ranging from approximately 21 to 35%) was noted in treated males and females of the two highest exposure groups (4.6 and 7.9 mg/kg/day), but not at lower exposure levels.

Significant brain AChE inhibition was noted at 4.6 and 7.9 mg/kg/day in females (magnitude 25.5 and 34.7%, respectively). High-dose males exhibited 24.8% brain AChE inhibition (not statistically significant). Although serum amylase activity was generally increased in diazinon-treated male and female dogs at most timepoints, the only statistically significant increase occurred in 4.6 mg/kg/day males only at week 52. There were no other treatment-related effects on clinical chemistry parameters examined. Ophthalmoscopic examinations, hematology, and urinalysis did not reveal evidence of treatment-related effects. There were no apparent treatment-related effects on organ weights and extensive gross and microscopic examinations were unremarkable. This study identified a NOAEL of 0.5 ppm (0.017 mg/kg/day) and a LOAEL of 150 ppm (4.6 mg/kg/day) for RBC AChE inhibition of 20% or more in both male and female dogs.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.; Carolyn Harper, Ph.D.; Paula Burgess, M.D.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

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

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

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

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

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

LEGEND

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

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

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

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

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

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

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

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

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

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

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

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

LEGEND

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

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

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

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

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

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

SAMPLE

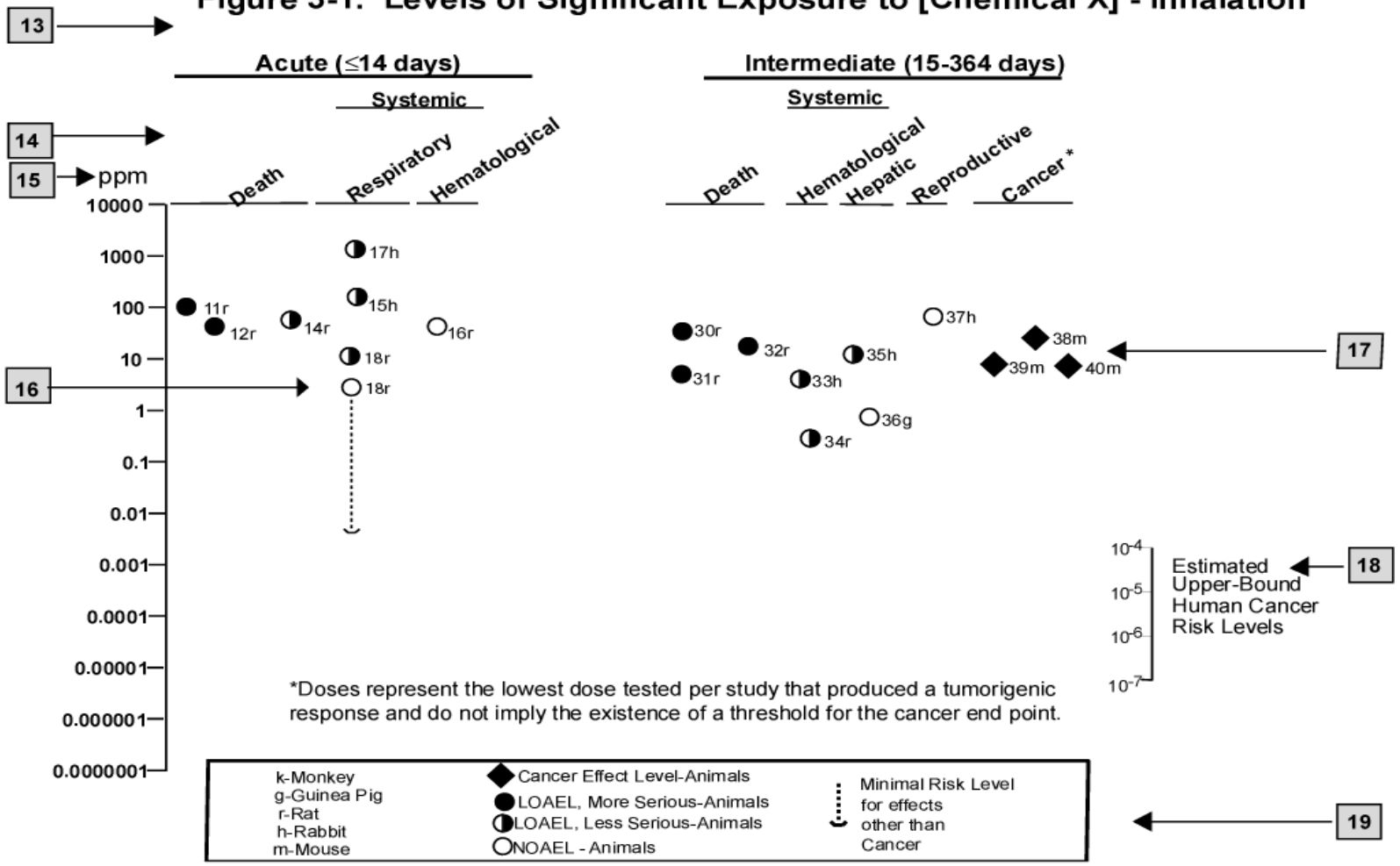
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

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



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

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

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

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APPENDIX D. INDEX

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