

TOXICOLOGICAL PROFILE FOR DIAZINON

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

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DISCLAIMER

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

UPDATE STATEMENT

A Toxicological Profile for 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:

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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.

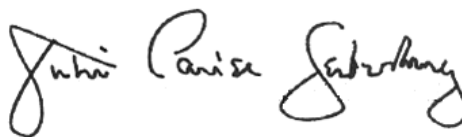
The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

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.



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*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.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.
2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
3. Data Needs Review. The 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.

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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 • Water and soil • Plants and animals	Diazinon is rapidly broken down to a number of different compounds. Diazinon is quickly broken down in a few hours to 2 weeks. 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.

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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.
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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.

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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.

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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 where 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.

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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.

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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 ($\mu\text{g/L}$) 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 $\mu\text{g/L}$ 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

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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

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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 bronchorecretion, 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,

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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/m³.

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/m³, 6 hours/day, 5 days/week for 3 weeks resulted in 36–39% RBC AChE inhibition in rats.

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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

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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/m³. 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/m³ 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/m³ 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

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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/m³) 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/m³ 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/m³ and in females at exposure levels ≥ 0.46 mg/m³. 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/m³ and in female rats at 1.57 and 11.6 mg/m³ (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/m³ group of female rats is below the level of inhibition considered to represent an adverse effect. Therefore, the 1.57 mg/m³ exposure level is a NOAEL and the highest exposure level (11.6 mg/m³) 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/m³ 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

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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

^astatistically significantly different from control (p≤0.01)

^bstatistically significantly different from control (p≤0.05)

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

Source: Hartman 1990

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reported, measures of variance (standard deviation or standard error) were not included in the report. The NOAEL of 1.57 mg/m³ 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:

$$\text{NOAEL}_{\text{ADJ}} = 1.57 \text{ mg diazinon/m}^3 \times 6 \text{ hours/24 hours} \times 5 \text{ days/7 days} = 0.28 \text{ mg diazinon/m}^3$$

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 RDDR_{ER}s.

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

$$\text{NOAEL}_{\text{HEC}} = \text{NOAEL}_{\text{ADJ}} \times \text{RDDR}_{\text{ER}} = 0.28 \text{ mg diazinon/m}^3 \times 1.558 = 0.44 \text{ mg diazinon/m}^3$$

The NOAEL_{HEC} of 0.44 mg/m³ 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/m³.

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%

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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

^aParameters 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/m³ 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/m³ 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

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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

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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

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

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

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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

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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.

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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

^aMean±standard error

Source: Singh 1988

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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,

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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 (μ mole/mL packed cells/minute) ^a	Percent RBC AChE inhibition
0	10	0.74 $\pm$ 0.05	
0.09	10	0.68 $\pm$ 0.07	8
0.18	10	0.67 $\pm$ 0.06	9
0.27	10	0.59 $\pm$ 0.04	20
0.36	10	0.58 $\pm$ 0.02	22

^aMean $\pm$ standard error

AChE = acetylcholinesterase; RBC = red blood cell

Source: Davies and Holub 1980a

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(2) homogeneous or nonhomogeneous variance, and (3) model mean fit. The resulting BMD₂₀ was 0.36 mg/kg/day and the BMDL₂₀ 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 BMDL₂₀ 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 BMDL₂₀ 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 BMDL₂₀ 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 BMDL₂₀ 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

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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

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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 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.

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).

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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.

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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 $\geq 60\%$ 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/m³ 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/m³ diazinon (nose-only) for 6 hours/day, 5 days/week for 3 weeks (Hartman 1990).

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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/m³ 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/m³ 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/m³, 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/m³ 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/m³ 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		Reference Chemical Form	Comments
					Less Serious (mg/m³)	Serious (mg/m³)		
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		Reference Chemical Form	Comments
					Less Serious (mg/m³)	Serious (mg/m³)		
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

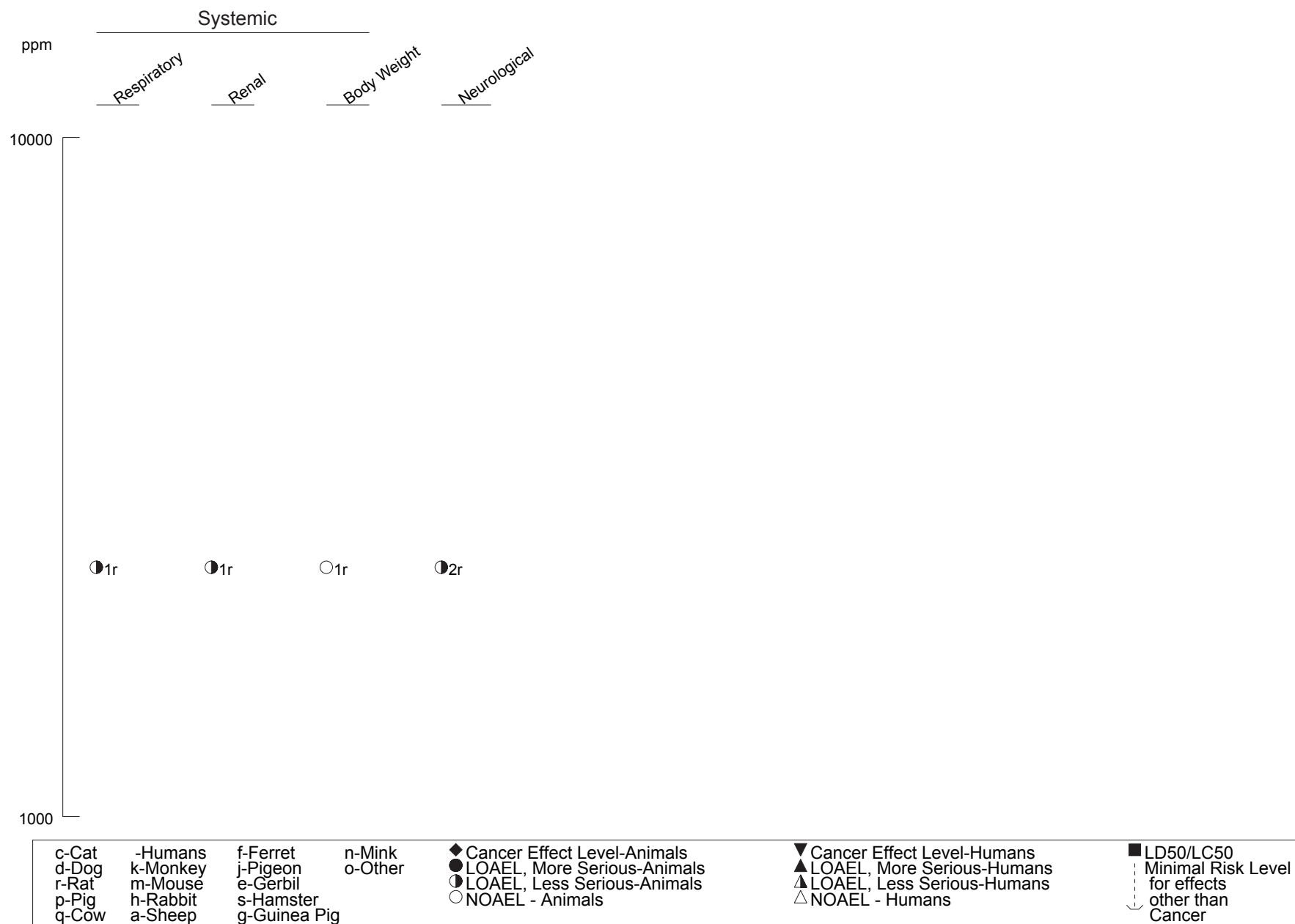
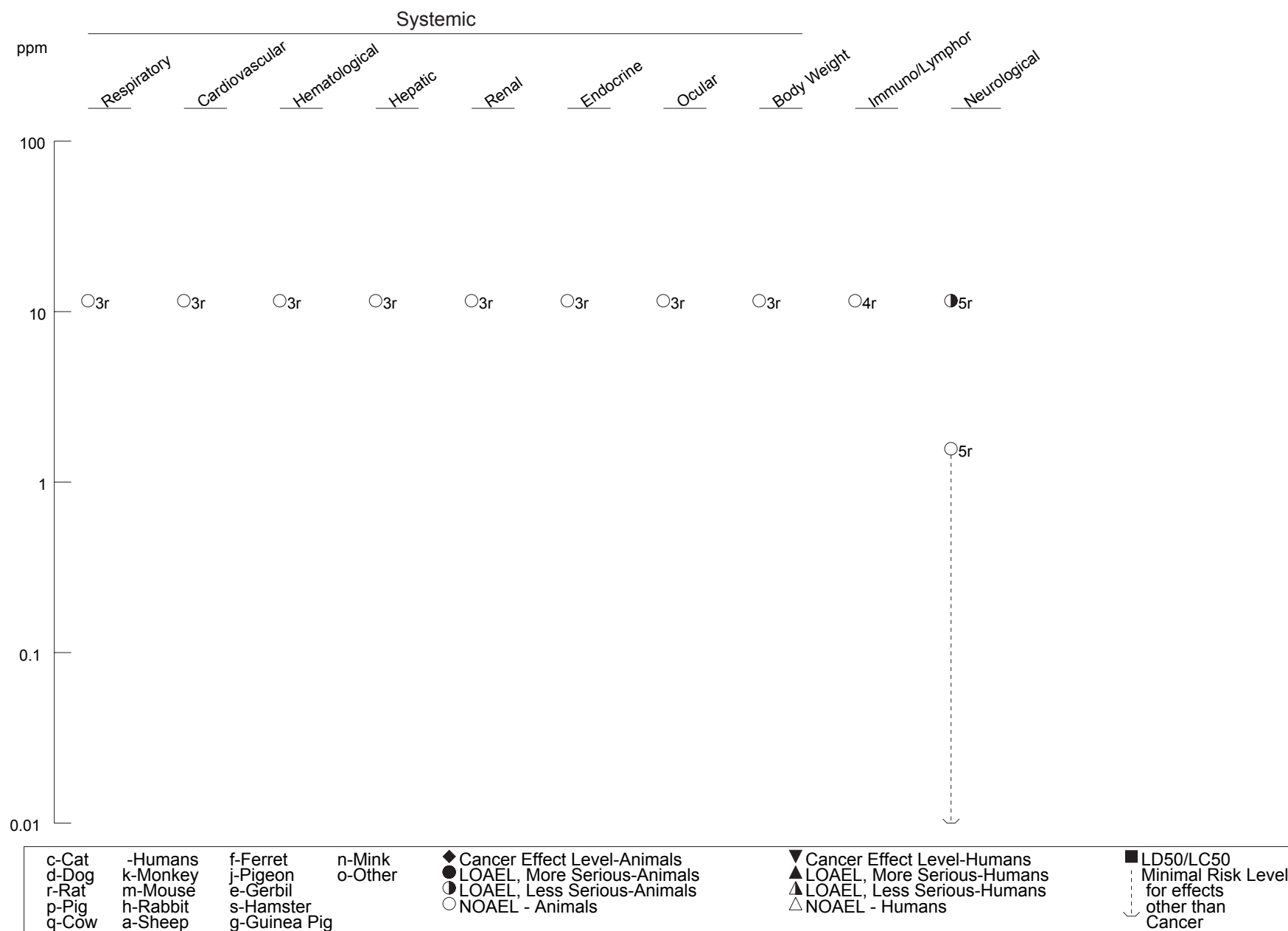
Acute (≤ 14 days)

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

Intermediate (15-364 days)



3. HEALTH EFFECTS

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/m³ 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/m³ 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/m³ 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/m³ 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/m³ 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/m³ 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/m³ 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/m³ 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/m³ 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. HEALTH EFFECTS

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 $\mu\text{g}/\text{m}^2$, air concentrations were between 5 and 27 $\mu\text{g}/\text{m}^3$, and some clothing showed contamination (0.5–0.7 $\mu\text{g}/\text{g}$). 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

3. HEALTH EFFECTS

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 cholinesterase 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/m³ 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/m³ 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/m³, respectively. No change was seen at 0.05 mg/m³. In males, no change was seen at 0.05 or 0.46 mg/m³, but decreases of 14 and 19% were seen at 1.57 and 11.6 mg/m³, respectively. RBC AChE activity (a surrogate marker for neural AChE) was unaffected in females at 0.05 and 0.46 mg/m³, but was decreased by 10 and 39% at 1.57 and 11.6 mg/m³, respectively. In males, no change was seen at 0.05, 0.46, or 1.57 mg/m³, while a decrease of 36% was observed at 11.6 mg/m³. Brain AChE activity was unchanged in males at all exposure levels, but was decreased in females at 0.05 mg/m³ (24%), 0.46 mg/m³ (17%), 1.57 mg/m³ (20%), and 11.6 mg/m³ (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.

3. HEALTH EFFECTS

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. HEALTH EFFECTS

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.

3. HEALTH EFFECTS

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 LD₅₀ values of 108 and 76 mg/kg were reported for male and female Sherman rats, respectively, whereas LD₅₀ 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 LD₅₀ 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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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 F (LD50) ^b	Gaines 1960	Technical grade diazinon (purity not specified).
7	Rat (Sherman)	once (GO)				250 M (LD50) ^b 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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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) 509 F (tachypnea, cyanosis)	Klemmer et al. 1978	
			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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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	^b 150 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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Neurological								
20	Human	once (IN)				^b 240 M (stupor, profuse diaphoresis, coma) 509 F (stupor, profuse diaphoresis, coma)	Klemmer et al. 1978	
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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
54	Rat (Sprague- Dawley)	13 wk 7 d/wk ad lib (F)	Resp	168 M ^b			Singh 1988	Diazinon MG-8 (purity 87.7%); concentrations in food adjusted for purity.
				212 F				
			Cardio	168 M ^b				
				212 F				
			Gastro	19 M	168 M ^b (soft stools)			
				15 F ^b	212 F (soft stools)			
			Hemato	168 M		212 F (decreased hemoglobin and hematocrit; increase in reticulocytes)		
				19 F ^b				
			Hepatic	168 M	212 F (increase in relative and absolute liver weight, minimal centrilobular hepatocellular hypertrophy)			
				19 F ^b				
			Renal	168 M ^b				
				212 F				
			Endocr	168 M ^b				
				212 F				
			Ocular	168 M ^b				
				212 F				
			Bd Wt	168 M ^b				
				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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
55	Rat (Sprague- Dawley)	6 wk 7 d/wk ad lib (F)	Gastro	^b 0.2 M 9.4 F	^b 8.4 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	^b 5.6 M 11.6 F		10.9 M (atrophy of pancreatic acini)		
			Ocular	11.6				
			Bd Wt	5.9 M ^b 0.21 F		10.9 M (34% decreased weight gain in males)		
						^b 5.6 F (33% decreased weight gain in females)		

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
58	Dog (Beagle)	8 mo 1 x/d (C)	Cardio	^b 5 M 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		^b 10 M (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	^b 5 M 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	^b 5 M	^b 10 M (significant weight loss)			
				10 F	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			Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)			
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 hypocellularity, increased myeloid element content)				
			Hepatic	1.25 (slight inflammation, occasional lobular congestion)	5 (interlobular connective tissue thickening, degenerative hepatocytes, hepatic hemorrhage)				
Immuno/ Lymphoret									
60	Rat (Sprague- Dawley)	13 wk 7 d/wk ad lib (F)		^b 168 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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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 ^d F	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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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		Reference	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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)		^b 168 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.

DIAZINON

3. HEALTH EFFECTS

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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
84	Dog (Beagle)	8 mo 1 x/d (C)		5 M		10 M (testicular atrophy, aspermato-genesis)	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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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		Reference	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
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)

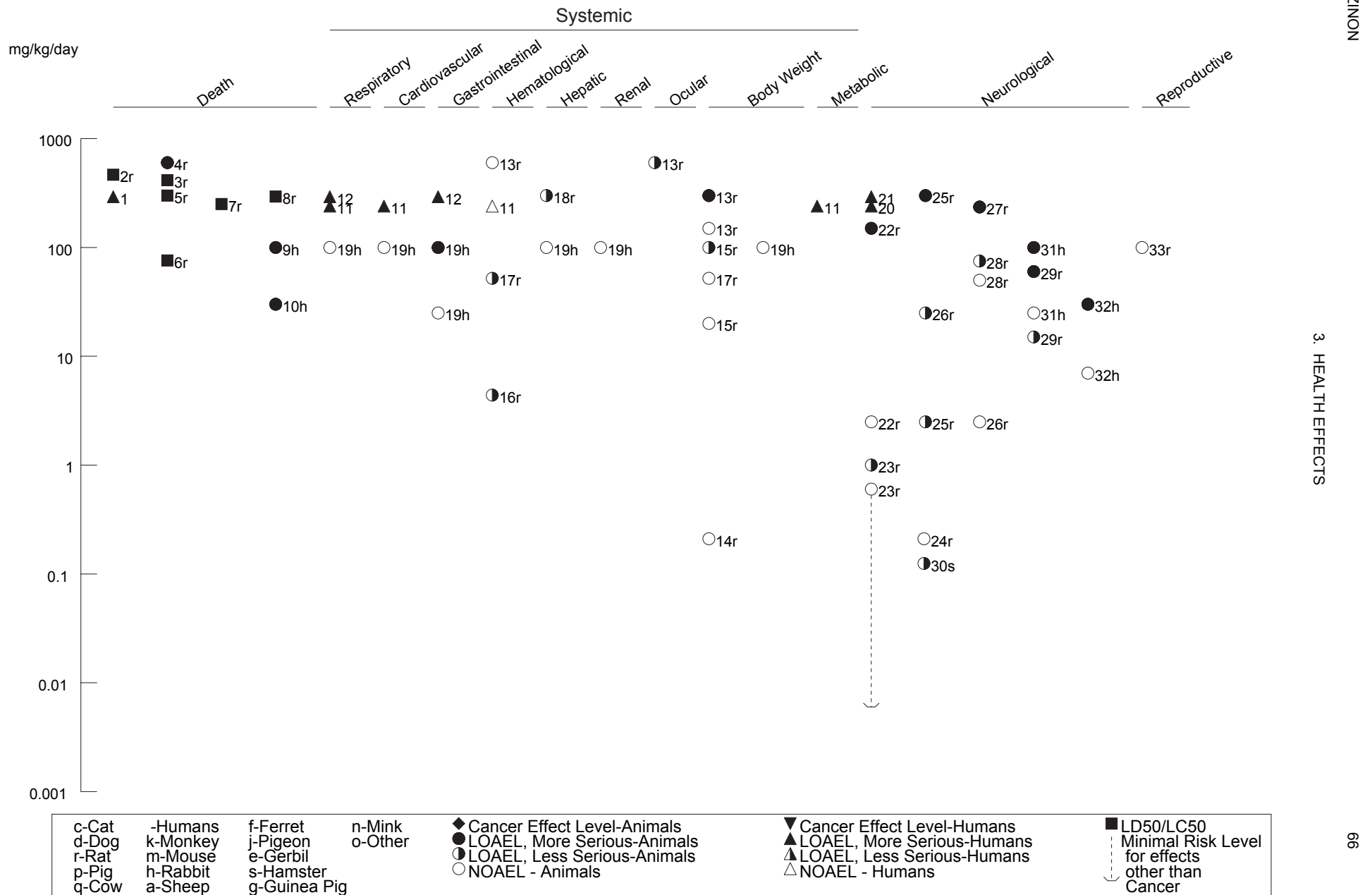


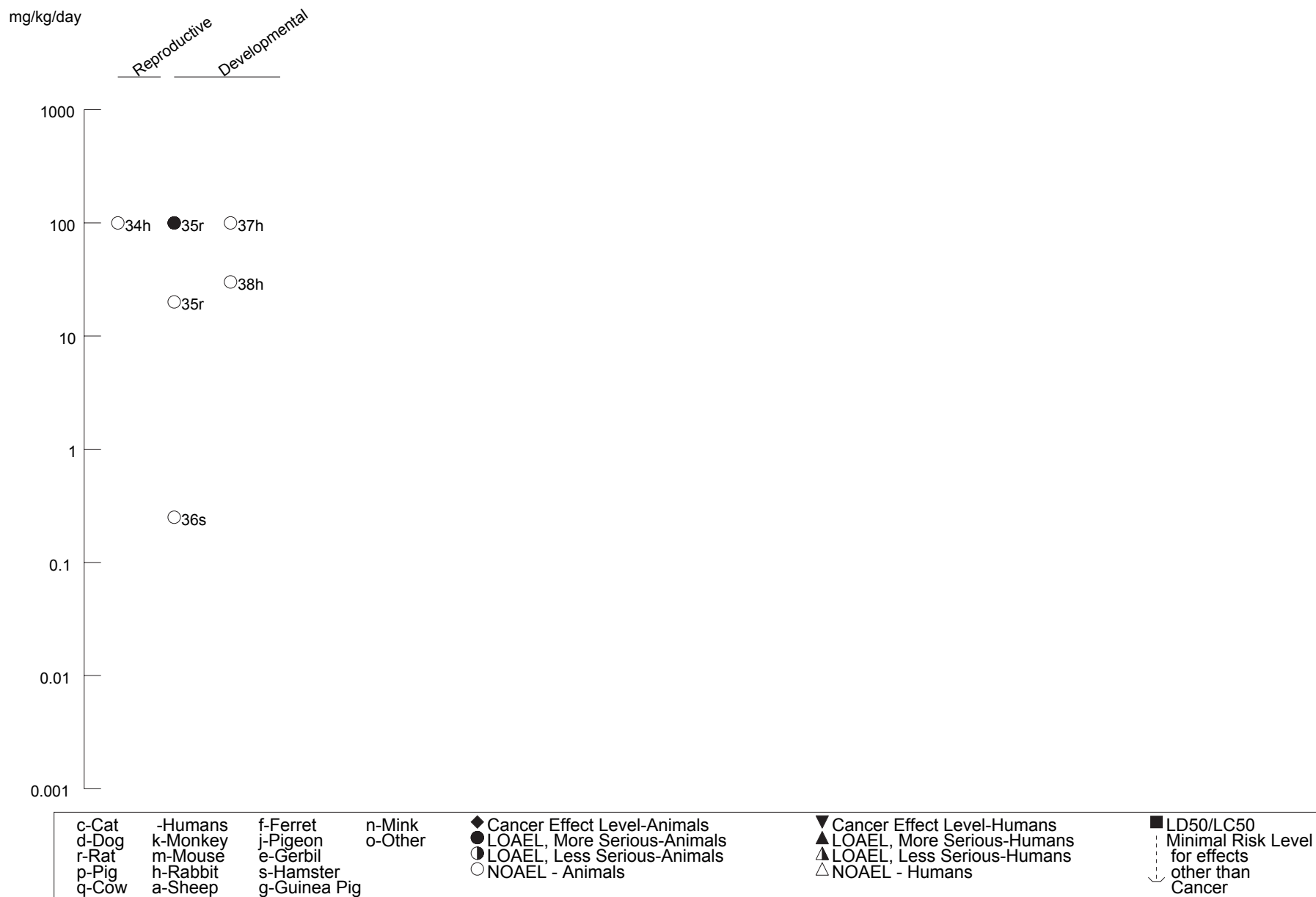
Figure 3-2 Levels of Significant Exposure to Diazinon - Oral (*Continued*)Acute (≤ 14 days)

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

Intermediate (15-364 days)

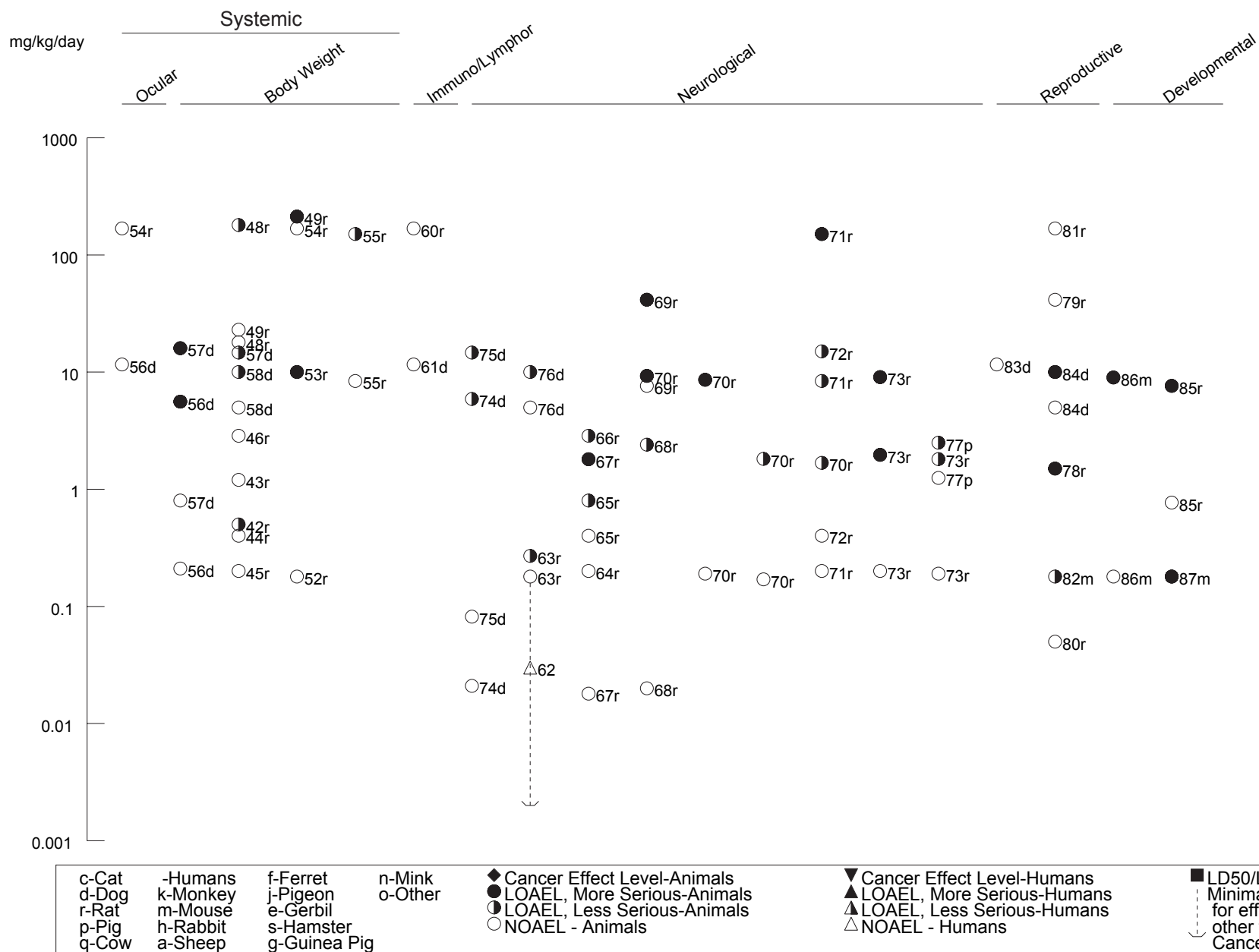
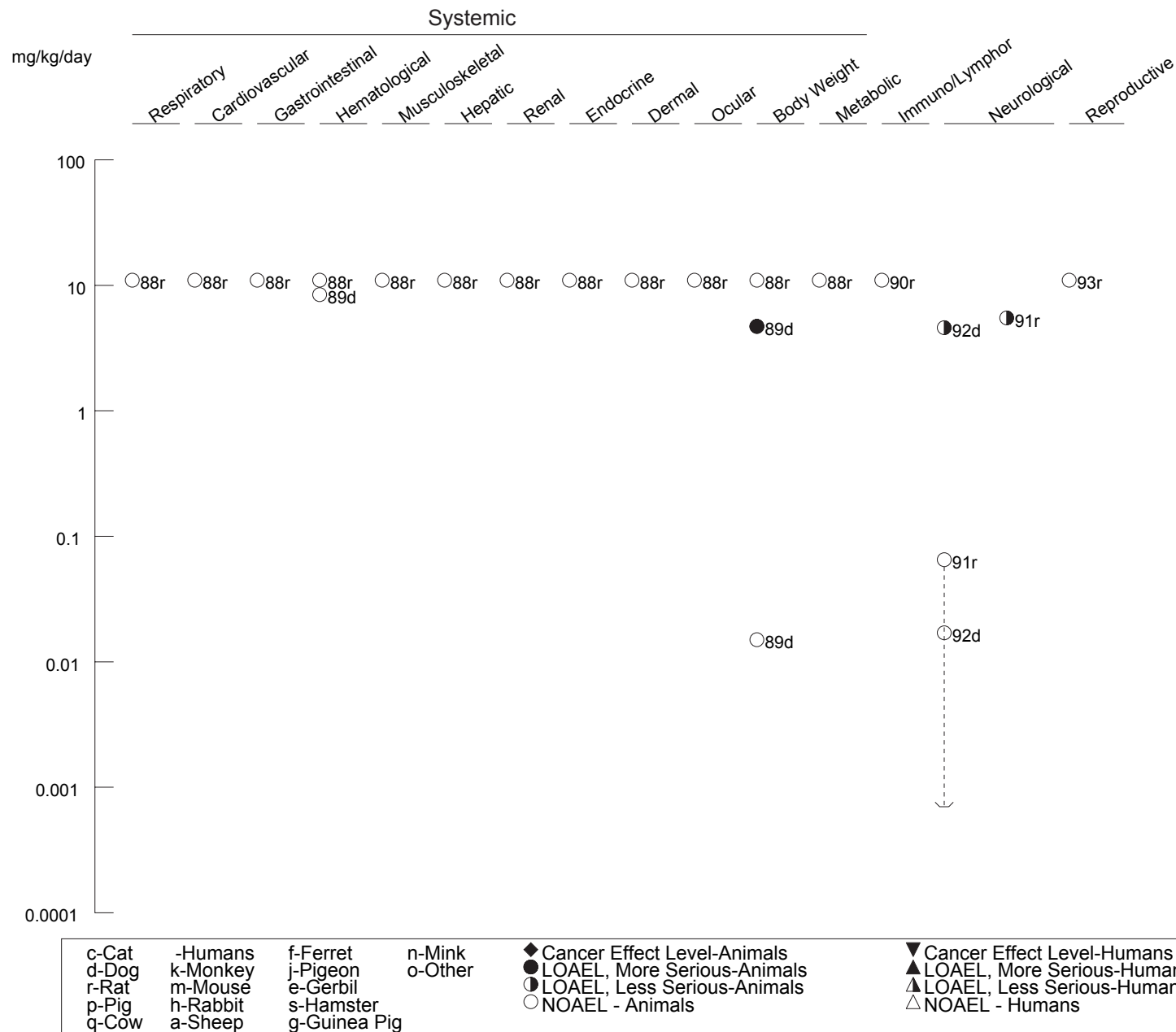


Figure 3-2 Levels of Significant Exposure to Diazinon - Oral (*Continued*)
Chronic (≤ 365 days)



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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).

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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

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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).

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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 ($694 \times 10^3/\text{mm}^3$ as compared to $856 \times 10^3/\text{mm}^3$). 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 hypercoagulability that, considered together with observations from other studies of various haemorrhagia, may

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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).

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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 aminotransferase, 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

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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 alkaluria, 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).

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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

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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

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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 administered 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 shrunk 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

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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 exclusively 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.

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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-

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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

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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

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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 (F₀–F₄). 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

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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

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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 IgG₁ 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 fetotoxic 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).

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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

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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 B6C3F₁ 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 B6C3F₁ 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 LD₅₀ values were determined in Sherman rats of both sexes (Gaines 1960). Diazinon was applied to a shaved dermal area of approximately 13.5 cm². LD₅₀ 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 LD₅₀ 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		Reference	Comments
				Less Serious	Serious		
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 (erythema) Percent (%)		Matsushita et al. 1985	Diazinon (purity not specified).
Rabbit (New Zealand)	4 hr	Dermal		0.5 B (erythema, colonies per slight edema) 100 milliliters		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)

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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

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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

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(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.

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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 μ M) causing slight AChE inhibition but not affecting cell viability (Flaskos et al. 2007).

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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

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

Species (test system)	End point	Results		References
		With activation	Without activation	
Prokaryotic organisms:				
<i>Bacillus subtilis</i> (rec assay)	Gene mutation	Not done	–	Shirasu et al. 1976
<i>Salmonella typhimurium</i>	Gene mutation	+	–	Wong et al. 1989
<i>S. typhimurium</i>	Gene mutation	Not done	–	Marshall et al.1976
<i>S. typhimurium</i>	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

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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 [¹⁴C]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 [¹⁴C]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

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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 cm² 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

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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.

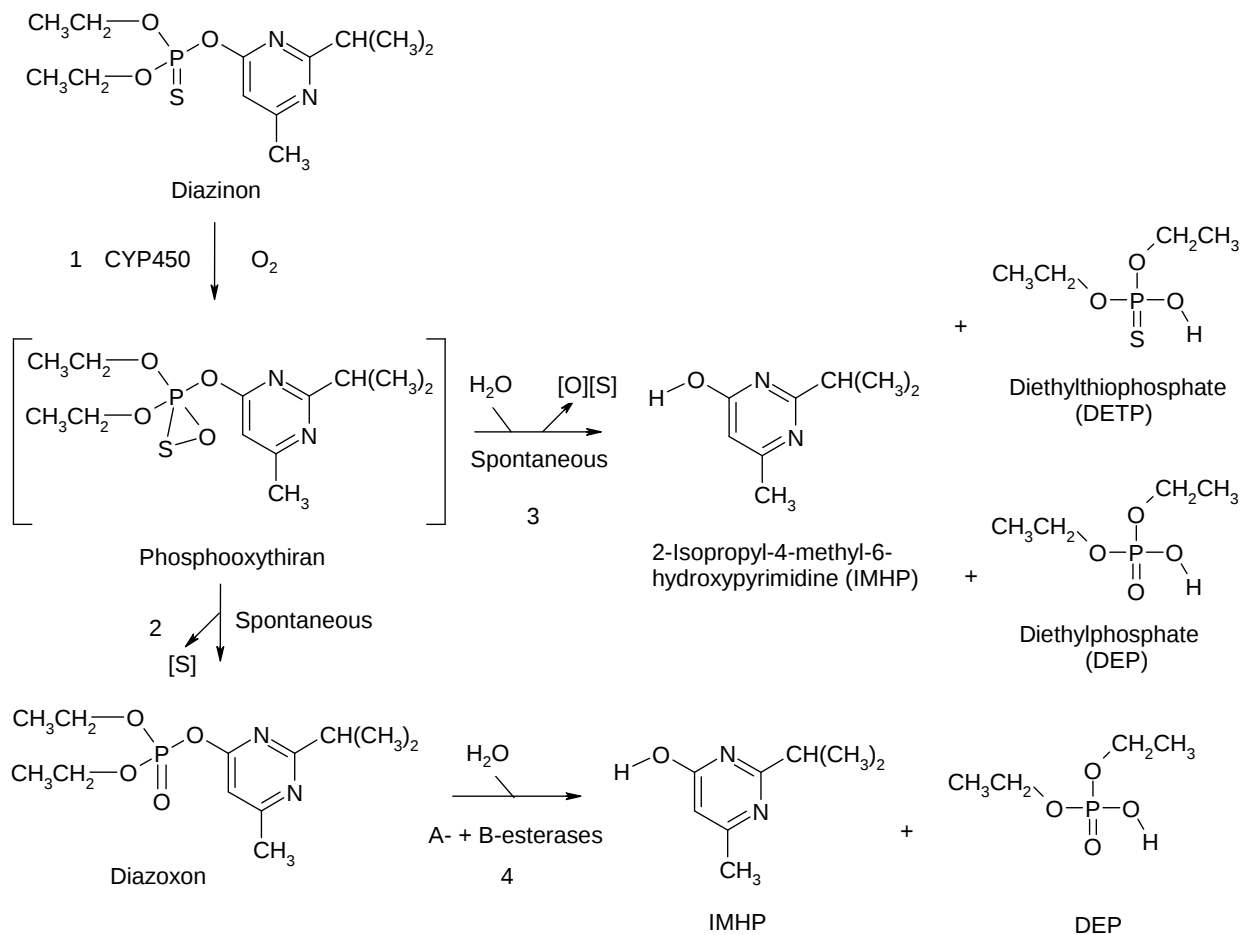
3.4.3 Metabolism

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, CYP2A2, 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.

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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

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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 $^{14}\text{CO}_2$ in expired air. No $^{14}\text{CO}_2$ 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 cm² 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

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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-¹⁴C]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 (Clewett 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

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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.

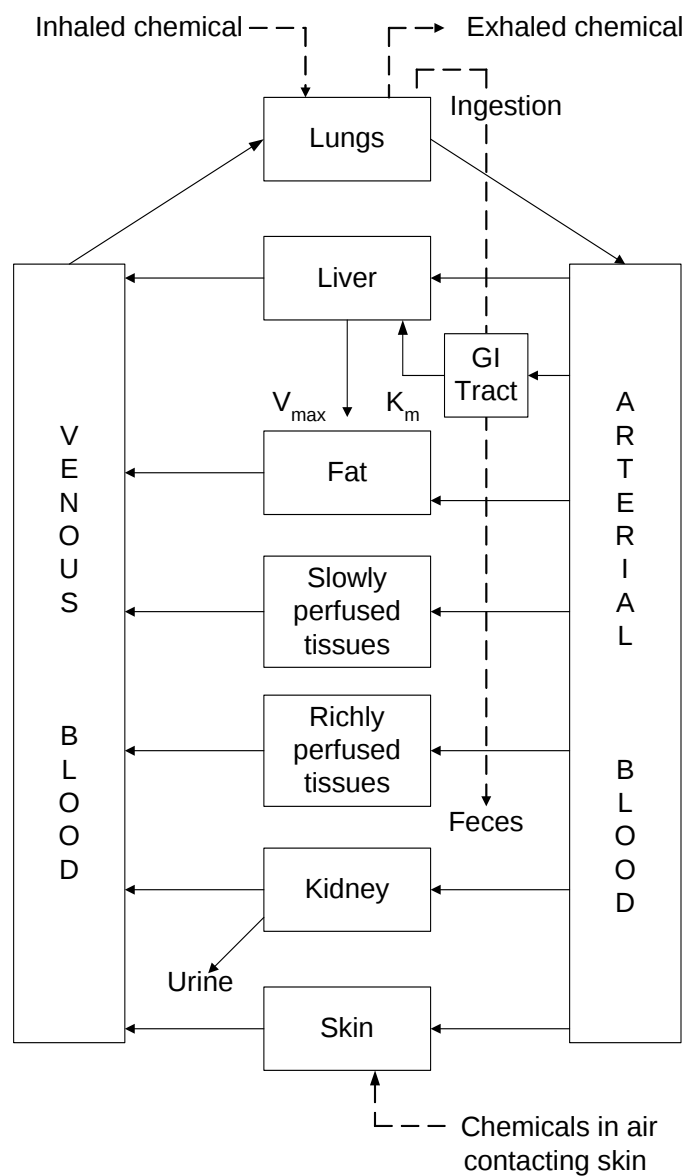
If PBPK models for diazinon exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

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.

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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.

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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.

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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

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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

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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.

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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 isoflavonoid 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;

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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 (1×10^{-4} M) (Nishihara et al. 2000). Results of the E-CALUX assay indicated a weakly positive response at a diazinon concentration of 4.6×10^{-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.

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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).

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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,

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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

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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

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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.

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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 CCl₄; alkenes, such as vinyl chloride; and allelic and acetylenic derivatives) may increase

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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 H₂ 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.

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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: McGraw-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.

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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

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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

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

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●				●			●	●
Oral	●	●			●	●			●	●
Dermal		●				●			●	●

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●		●	●				
Oral	●	●	●	●	●	●	●			●
Dermal	●	●	●		●	●				

Animal

● Existing Studies

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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

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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 LD₅₀ 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/m³. 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

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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;

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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

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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).

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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.

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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.

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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.

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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

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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.

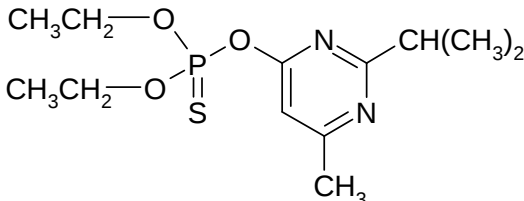
Manufacture of diazinon for indoor use products in the United States was discontinued as of March 1, 2001, and manufacture of non-agricultural outdoor use products was discontinued as of June 30, 2003 (HSDB 2008; WHO 1998).

4.2 PHYSICAL AND CHEMICAL PROPERTIES

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

4. CHEMICAL AND PHYSICAL INFORMATION

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 ₂ O ₃ PS	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

4. CHEMICAL AND PHYSICAL INFORMATION

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 2×10^{-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	9.01×10^{-5} mm Hg	HSDB 2008
at 40 °C ^b	1.1×10^{-3} mm Hg	O'Neil et al. 2001
Henry's law constant	1.17×10^{-7} atm-m ³ /mol	
Autoignition temperature	No data	HSDB 2008
Flashpoint	82.2 °C	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;

4. CHEMICAL AND PHYSICAL INFORMATION

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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.

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

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

^aPost office state abbreviations used^bAmounts on site reported by facilities in each state^cActivities/Uses:

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

Source: TRI05 2007 (Data are from 2005)

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

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

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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).

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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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6.1 OVERVIEW

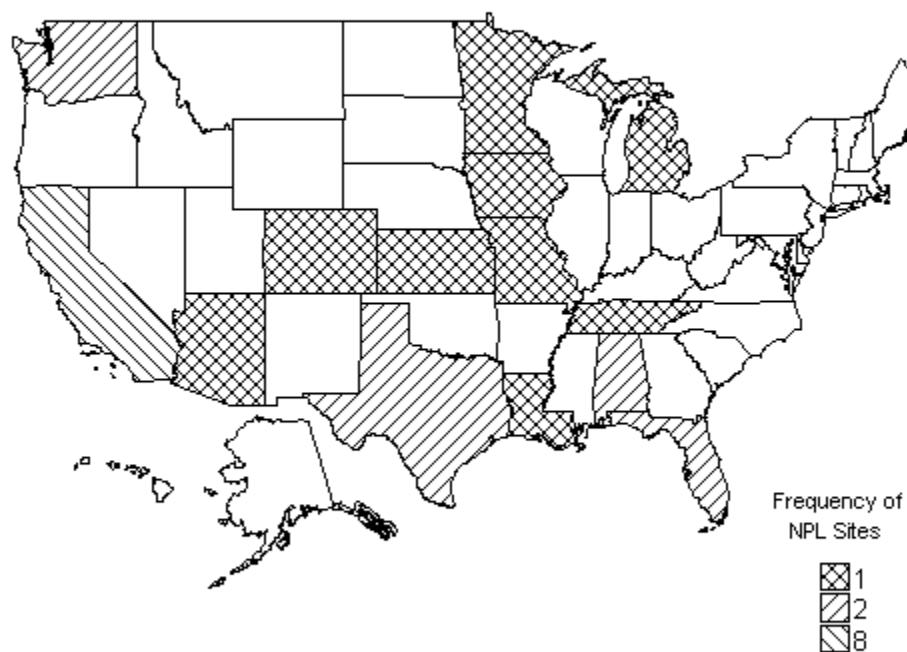
Diazinon has been identified in at least 25 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2008). However, the number of sites evaluated for diazinon is not known. The frequency of these sites can be seen in Figure 6-1. Of these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

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

Derived from HazDat 2008

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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

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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 $\geq 25,000$ pounds of any TRI chemical or otherwise uses $>10,000$ pounds of a TRI chemical in a calendar year (EPA 2005).

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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

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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).

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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

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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/m³, respectively, for samples collected at the 114 m elevation and 1.4–12 and 1.8–13 pg/m³, 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

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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

