

**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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UPDATE STATEMENT

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

FOREWORD

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

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audience for the toxicological profiles is 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.



David Satcher, M.D., Ph.D.
Administrator
Agency for Toxic Substances and
Disease Registry

Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on April 29, 1996 (61 FR 18744). 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); and February 28, 1994 (59 FR 9486). Section 104(I)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Alfred Dorsey, D.V.M.
ATSDR, Division of Toxicology, Atlanta, GA

James Corcoran, Ph.D.
Research Triangle Institute, Research Triangle Park, NC

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

- 1 . Green Border Review. Green Border review assures consistency with ATSDR policy.
- 2 . 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.
- 3 . 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.

PEER REVIEW

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

1. Dr. Morris Cranmer, Private Consultant, Cranmer & Associates, Little Rock, Arkansas;
2. Dr. Donald Morgan, Private Consultant, Iowa City, Iowa; and
3. Dr. Josef Seifert, Professor of Environmental Biochemistry, University of Hawaii, Honolulu, Hawaii.

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. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

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

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1. PUBLIC HEALTH STATEMENT

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

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up. Diazinon has been found in at least 18 of the 1,430 current or former NPL sites. However, it's unknown how many NPL sites have been evaluated for this substance. As more sites are evaluated, the sites with diazinon may increase. This is important because exposure to this substance may harm you and because these sites may be sources of exposure.

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

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

1.1 WHAT IS DIAZINON?

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. It is also used to control household pests such as flies, fleas, and cockroaches. This chemical is synthetic and does not occur naturally in the environment. Diazinon is sold under common trade names including Alfatox, Basudin, AG 500, Dazzel, Gardentox, and Knoxout.

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The pure chemical (100% diazinon) is a colorless and practically odorless oil. Preparations used in agriculture and by exterminators contain 85-90% diazinon and appear as a pale to dark-brown liquid. This form of diazinon is diluted with other chemicals before use. The diazinon available for home and garden use contains 1-5% diazinon in a liquid or as solid granules. These preparations have a slight chemical odor but cannot be identified by smell. Most of the diazinon used is in liquid form, but it is possible to be exposed to the chemical in a solid form. Diazinon does not burn easily and does not dissolve easily in water. It will dissolve in alcohol or other organic solvents such as petroleum products. Its basic physical and chemical properties are summarized in Chapter 3; for more information on its production and use, see Chapter 4.

1.2 WHAT HAPPENS TO DIAZINON WHEN IT ENTERS THE ENVIRONMENT?

Diazinon may enter the environment during the manufacturing process, but most environmental contamination comes from agricultural and household application of the chemical to control insects. Diazinon is often sprayed on crops and plants, so small particles of the chemical may be carried away from the field or yard before falling to the ground. Studies have not shown harmful human health effects resulting from airborne contamination of areas surrounding fields where diazinon has been used. After diazinon has been applied, it may be present in the soil, surface waters (such as rivers and ponds), and on the surface of the plants. Diazinon on soil and plant surfaces may also be washed into surface waters by rain. Up to 25% of applied diazinon can return to the air from the surface where it was applied. In the environment, diazinon is rapidly broken down into a variety of other chemicals. Depending on the soil or water conditions, the time required for one-half of the diazinon to be broken down is between a few hours and 2 weeks. Diazinon can move through the soil and contaminate ground water (water below the surface such as well water). Diazinon is rapidly broken down by most animals that eat it. This means the chemical is not likely to build up to high or dangerous levels in animal or plant foods that you might eat. For more information on diazinon use and its fate in the environment, see Chapters 4 and 5.

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1.3 HOW MIGHT I BE EXPOSED TO DIAZINON?

Diazinon can be bought at any home or garden supply store in the United States and is safe if used according to the directions printed on the container. Small amounts of diazinon have been detected in foods sold to consumers, but studies by the Food and Drug Administration (FDA) have found that the levels in food are far below the level that might cause any harmful health effects. Diazinon has been found in surface and ground water samples collected at many locations. Only a few of these samples contained high levels of diazinon contamination. These were associated with runoff from contaminated fields or single sources responsible for contamination such as illegal dumping. In areas surrounding hazardous waste disposal or treatment facilities, you could be exposed by contact with contaminated soils or contaminated runoff water or ground water that resulted from spills or leaks of material on the site. People who work in the manufacture and professional application of diazinon have the most significant exposure to this insecticide. Other than people who are exposed at work, those most likely to be exposed are people who use the chemical on lawns or gardens, or to control insects in the home. For more information on the ways people might be exposed to diazinon, see Chapter 5.

1.4 HOW CAN DIAZINON ENTER AND LEAVE MY BODY?

If you breathe air containing diazinon, you may absorb it into your body through your lungs. If you eat food or drink water containing diazinon, the chemical may be absorbed from your stomach and intestines. Diazinon may also enter your body across the skin. People living near hazardous waste sites are most likely to be exposed to diazinon through contact with contaminated soil or runoff water.

Once in the body, diazinon is rapidly broken down and eliminated from the body in both the urine and feces. Diazinon has not been shown to accumulate in any tissues and almost all of the chemical is eliminated from the body in 12 days. For more information, see Chapter 2.

1. PUBLIC HEALTH STATEMENT

1.5 HOW CAN DIAZINON AFFECT MY HEALTH?

Most cases of unintentional diazinon poisoning in people have resulted from short exposures to very high concentrations of the material. Usually this occurs when workers who use the chemical do not properly protect themselves, and when they inhale, swallow, or contaminate their skin with a large amount of diazinon. Whether you have harmful effects to your health from diazinon exposure depends on how much you are exposed to and for how long you are exposed. Diazinon affects the nervous system. Some mild symptoms of exposure are headache, dizziness, weakness, feelings of anxiety, constriction of the pupils of the eye, and not being able to see clearly. If you experience these symptoms, you should seek medical attention immediately. Emergency rooms have drugs that stop the harmful effects of diazinon. More severe symptoms include nausea and vomiting, abdominal cramps, slow pulse, diarrhea, pinpoint pupils, difficulty in breathing, and passing out (coma). These signs and symptoms may start to develop within 30-60 minutes of the exposure and reach their maximum at about 6-8 hours. Very high exposure to diazinon has resulted in death in people accidentally exposed and in those who have swallowed large amounts of the chemical to commit suicide. Damage to the pancreas has developed in some people and in laboratory animals exposed to large amounts of diazinon. Longer exposure to lower levels of diazinon has also been reported to produce some of these symptoms in exposed workers and in people living in houses recently treated with the chemical to control pests. In almost all cases, complete recovery occurred when the exposure stopped. There is no evidence that long-term exposure to low levels of diazinon causes any harmful health effects in people. Diazinon has not been shown to cause birth defects or to prevent conception in humans. Diazinon has not been shown to cause cancer in people or animals. The International Agency for Research on Cancer (IARC), the Environmental Protection Agency (EPA), and the National Toxicology Program (NTP) have not officially classified diazinon as to its carcinogenicity.

In animal studies, high doses of diazinon produced effects on the nervous system similar to those seen in people. For more information on the health effects of diazinon, see Chapter 2.

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

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 (serum 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. This test requires only a small amount of blood and is routinely available in your doctor's office. 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. Other chemicals or disease states may also alter the activity of this enzyme. There is a wide range of normal cholinesterase activity in the general population. If you have not established your normal or baseline value through a previous test, you might have to repeat the test several times to determine if your enzyme activity is recovering.

Specific tests are available to determine the presence of diazinon or its breakdown products in blood, body tissue, and urine. These tests are not routinely available through your doctor's office and require special equipment and sample handling. If you need the specific test, your doctor can collect the sample and send it to a special laboratory for analysis. This test is 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. For more information on how to determine if you have been exposed to diazinon, see Chapters 2 and 6.

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

The federal government has set standards and guidelines to protect people from the possible harmful health effects of diazinon. The Environmental Protection Agency (EPA) has

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developed 1- and 10-day health advisories (maximum recommended drinking water concentrations) for adults and children of 20 micrograms per liter of water. The lifetime health advisories determined for both children and adults are 0.6 micrograms per liter of drinking water. The EPA has also set tolerances for residues of diazinon in various raw food products of 0.1-60 parts of diazinon per million parts of food (ppm). The National Institute for Occupational Safety and Health (NIOSH) recommends an occupational exposure limit (time-weighted average [TWA]) of 0.1 milligram per cubic meter of air based on working 8 hours per day for 40 hours per week. For more information on regulations and guidelines to protect human health, see Chapter 7.

1.8 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:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333
(404) 639-6000

This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 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 of 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.

2.2 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. 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 lowestobserved-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

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

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

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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.

2. HEALTH EFFECTS

2.2.1 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).

2.2.1.1 Death

There are no reports of deaths in humans or animals exposed by inhalation to diazinon alone. But one clinical study reported human death following inhalation exposure to an insecticide mixture that contained diazinon and malathion, another anticholinesterase insecticide. A 51-year-old man died from cardiac arrest, despite atropine therapy, following inhalation exposure to a commercial insecticide formulation containing diazinon and malathion. 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 acetylcholinesterase activity was one-half that of muscle from unexposed persons (Wecker et al. 1985).

No deaths were reported in Sprague-Dawley rats (5 of each 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 (groups of 10 of each sex) exposed to air concentrations of 0.05, 0.46, 1.57, or 11.6 mg/m³ diazinon (nose-only) for 6 hours a day, 5 days a week for 3 weeks (Hartman 1990).

2.2.1.2 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 1985). No studies were located regarding gastrointestinal, musculoskeletal, dermal, or metabolic 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

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for systemic end points in each species and duration category are recorded in Table 2-1 and plotted in Figure 2- 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 3 weeks, 5 days a week for 6 hours a day (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 at any concentration of diazinon.

Cardiovascular Effects. No gross or histological evidence of treatment-related damage to the heart was observed in hybrid rats (10 of each sex) exposed to 11.6 mg/m³ diazmon (nose-only) for 3 weeks, 5 days a week for 6 hours a day (Hartman 1990).

Hematological Effects. No statistically significant differences in hematological parameters (erythrocyte count, hemoglobin, packed red cell volume) were seen compared to controls in hybrid rats (10 of each sex) exposed to up to 11.6 mg/m³ diazinon (nose-only) for 3 weeks, 5 days a week for 6 hours a day (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 acetylcholinesterase activity was one-half that of muscle from unexposed persons (Wecker et al. 1985).

Hepatic Effects. - No gross or histological evidence of treatment-related damage to the liver was observed in hybrid rats (10 of each sex) exposed to 11.6 mg/m³ diazinon (nose-only) for 3 weeks, 5 days a week for 6 hours a day (Hartman 1990).

Renal Effects. Polyuria was observed in Sprague-Dawley rats exposed to 2,330 mg/m³ for 4 hours (Holbert 1989). No gross or histological evidence of treatment-related damage to the kidney was

Table 2-1. Levels of Significant Exposure to Diazinon - Inhalation

Key to figure ^a	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference
					Less serious (mg/m3)	Serious (mg/m3)	
ACUTE EXPOSURE¹							
Systemic							
1	Rat (Sprague- Dawley)	4 hr	Resp		2330 M (nasal discharge; 3/5)		Holbert 1989
			Renal Bd Wt	2330	2330 F (polyuria; 3/5)		
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			
Immunological/Lymphoreticular							
4	Rat (Hybrid)	3 wk 5 d/wk 6 hr/d		11.6			Hartman 1990

Table 2-1. Levels of Significant Exposure to Diazinon - Inhalation (continued)

Key to figure	Species (strain)	Exposure/ duration/ frequency	System	LOAEL			Reference
				NOAEL (mg/m ³)	Less serious (mg/m ³)	Serious (mg/m ³)	
Neurological							
5	Rat (Hybrid)	3 wk 5 d/wk 6 hr/d		0.46 ^b F	1.57 F (20% decrease in brain AChE)		Hartman 1990

^aThe number corresponds to entries in Figure 2-1.

^bUsed to derive an intermediate-duration Minimal Risk Level (MRL) of 0.009 mg/m³; based on the NOAEL of 0.46 mg/m³ for brain acetylcholinesterase inhibition; concentration adjusted for intermittent exposure, converted to a human equivalent concentration, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

AChE = acetylcholinesterase; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; gen = generation; Hemato = hematological; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s)

Figure 2-1. Levels of Significant Exposure to Diazinon - Inhalation
 Acute (≤ 14 days)

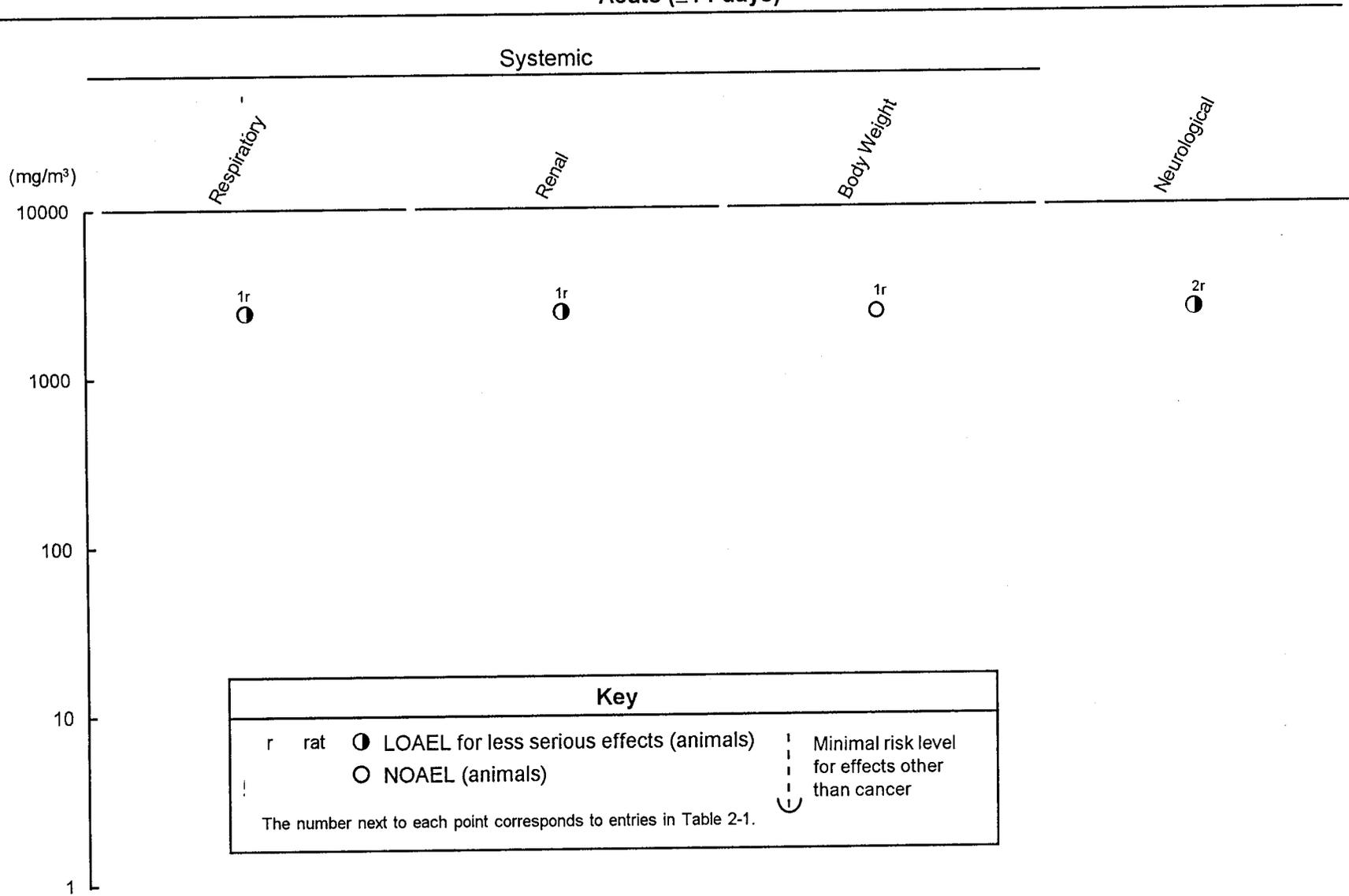
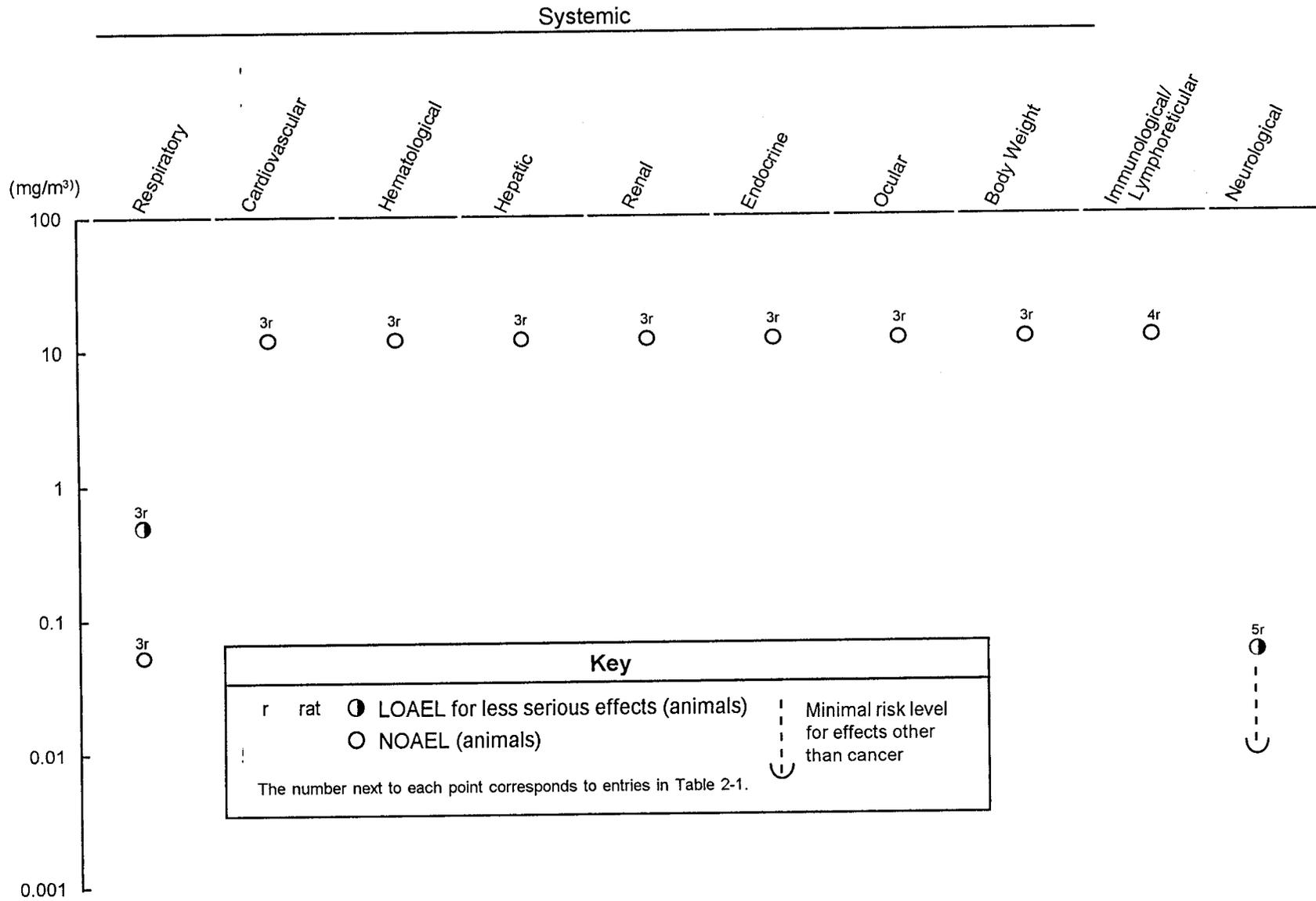


Figure 2-1. Levels of Significant Exposure to Diazinon - Inhalation (cont.)

Intermediate (15-364 days)



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observed in hybrid rats (10 of each sex) exposed to 11.6 mg/m³ diazinon (nose-only) for 3 weeks, 5 days a week for 6 hours a day (Hartman 1990).

Endocrine Effects. No gross or histological evidence of treatment-related damage to the adrenal gland was observed in hybrid rats (10 of each sex) exposed to 11.6 mg/m³ diazinon (nose-only) for 3 weeks, 5 days a week for 6 hours a day (Hartman 1990).

Ocular Effects. Ptosis was observed in Sprague-Dawley rats exposed to 2,330 mg/m³ for 4 hours in an inhalation chamber (Holbert 1989). No evidence of treatment-related ophthalmoscopic lesions was observed in hybrid rats (10 of each sex) exposed to up to 11.6 mg/m³ diazinon (nose-only) for 3 weeks, 5 days a week for 6 hours a day (Hartman 1990).

Body Weight Effects. No effect on body weight was observed in Sprague-Dawley rats (5 of each sex) exposed to 2,330 mg/m³ for 4 hours and observed for a further 14 days (Holbert 1989) or in hybrid rats (10 of each sex) exposed to up to 11.6 mg/m³ diazinon (nose-only) for 3 weeks, 5 days a week for 6 hours a day (Hartman 1990).

2.2.1.3 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 of each sex) exposed to 11.6 mg/m³ diazinon (nose-only) for 3 weeks, 5 days a week for 6 hours a day (Hartman 1990).

The NOAEL for immunological and/or lymphoreticular end points in hybrid rats for intermediateduration exposure is recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.4 Neurological Effects

Diazinon, an anticholinesterase organophosphate, inhibits acetylcholinesterase in the central and peripheral nervous system. Inhibition of acetylcholinesterase results in accumulation of acetylcholine

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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 all but one of 18 mushroom workers exposed to diazinon sprayed around the only entrance to a room in which they were working. The workers exhibited reduced serum and erythrocyte cholinesterase levels (markers for diazinon exposure) within 48 hours; serum cholinesterase levels were inhibited 27-29% by diazinon exposure within 15 days post-exposure (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 house had been treated with diazinon, analysis of the family members' urine samples showed "very high urinary levels" (0.5-1.5 mg/L) of a diazinon metabolite, diethyl phosphate (DEP), while serum cholinesterase levels were slightly depressed (79-94% of normal levels). Surface concentrations 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 clean-up 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 per day for 39 days during an insecticide application program reported only slight neurological functional deficits (post-shift 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 serum cholinesterase levels indicating exposure (Stalberg et al. 1978). In contrast, organophosphate poisoning-induced increases in hyperreflexia were reported in workers occupationally exposed to many insecticides, including diazinon. These workers, however, showed no overt signs of poisoning or of cholinergic signs and symptoms after spraying diazinon (Rayner et al. 1972). Two

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other insecticide sprayers developed cholinergic symptoms after spraying diazinon. Symptoms included nausea, vomiting, muscle twitching, difficulty breathing, and blurred vision. Serum and erythrocyte cholinesterase 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.

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 3 weeks, 5 days a week for 6 hours a day (Hartman 1990). At study termination, serum cholinesterase 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 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. Erythrocyte acetylcholinesterase activity (a surrogate marker for neural acetylcholinesterase) 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 acetylcholinesterase 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 erythrocyte acetylcholinesterase 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 besides piloerection were not observed in either sex.

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

The highest NOAEL and all LOAEL values from each reliable study for neurological end points in each species and duration category are recorded in Table 2-1 and plotted in Figure 2- 1.

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2.2.1.5 Reproductive Effects

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

2.2.1.6 Developmental Effects

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

2.2.1.7 Genotoxic Effects

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 non-exposed 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. Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 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. Thus, it is not possible to attribute the increased cancer incidence exclusively to diazinon exposure. Some of the exposure is presumed to have occurred by the inhalation route.

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 non-farmers. The report attributed the increased incidence of lymphomas to handling of organophosphorus insecticides,

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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.

2.2.2 Oral Exposure

2.2.2.1 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 acetylcholinesterase 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 (De Palma et al. 1970). The estimated dose of diazinon in this case was

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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.

A group of 8 children who accidentally became intoxicated by eating oatmeal contaminated with diazinon all recovered (Reichert et al. 1977). A dose could not be determined in this case, but typical neurological signs of diazinon toxicity were observed. Five individuals who intentionally ingested doses of 240-916 mg/kg diazinon recovered after treatment (Klemmer et al. 1978).

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, and age, and other modifying factors such as diet. It is likely that earlier formulations were more toxic to experimental animals than current ones because of the formation of toxic breakdown products (e.g., sulfotepp) in unstabilized diazinon (Hayes 1982).

In laboratory animal studies, single oral diazinon doses of 50-700 mg/kg to rats resulted in respiratory distress (from pulmonary inflammation and occasional extensive pneumonitis), vascular congestion, and venous stasis in the treated rats. Death generally resulted from respiratory failure that was usually preceded by coma (Boyd and Carsky 1969). A recent study on male Sprague-Dawley rats demonstrated that animals receiving a single oral gavage dose of 2,000 mg/kg diazinon died within 12 hours of dosing, while doses of 500 mg/kg or 1,000 mg/kg did not cause death (Takahashi et al. 1991). The oral LD₅₀ dose (lethal dose, 50% kill) of diazinon was determined in white male rats to be 300 mg/kg (Enan et al. 1982).

Oral LD₅₀ values for Sherman albino rats were determined to be 108 mg/kg and 76 mg/kg for males and females, respectively, indicating that female rats appear to be more sensitive than male rats (Gaines 1960). When Sherman rats were used, diazinon was less toxic than an earlier report which suggested that males were more sensitive than females, with LD₅₀ values of 250 mg/kg and 285 mg/kg for males and females, respectively (Gaines 1969). Another study determined the oral LD₅₀ values for male rats for an emulsified solution and wetttable paste preparations of diazinon to be 408 and 293 mg/kg, respectively. Males were also found to be the more sensitive sex in a preliminary experiment in this study. Clinical signs of intoxication seen in the dying rats were indicative of cholinergic effects (muscular fibrillation, salivation, lacrimation, incontinence, diarrhea, respiratory distress, hypothermia, prostration, convulsions, gasping, and coma) (Edson and Noakes 1960). An

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LD₅₀ of 10.9 mg/kg was determined for Red Heavy chickens as part of a delayed neurotoxicity study (Jenkins 1988). The low LD₅₀ for chickens reported in this study reflects the relative lack of organophosphate metabolizing enzymes in birds compared to mammals.

The effect of dietary protein on diazinon toxicity was evaluated in a study with male albino Wistar rats. The study concluded that a purified protein test diet (with 26% casein and 59% cornstarch) did not significantly alter the LD₅₀ value (415 mg/kg) for diazinon for this species. However, a low protein purified test diet (3.5% casein, 82% cornstarch), lowered the LD₅₀ to 215 mg/kg. In addition, this study found that diazinon samples that were time-of-manufacture stabilized (to prevent spontaneous degradation to more toxic monothiotetraethyl pyrophosphate) were less toxic (LD₅₀ value = 466 mg/kg) than samples stabilized after manufacture (LD₅₀ value = 271 mg/kg) (Boyd and Carsky 1969). A subsequent study examined the effect of isocaloric diets varied in protein concentration (as casein) from 0% to 81% casein in male albino Wistar rats. The study concluded that while varying dietary protein content from 13 to 3 12% of the normal amount increased acute lethality by 2-fold or less, a protein-free diet resulted in a 7.5-fold increase (although some of this lethality may have resulted from diazinon-induced anorexia and the particular sensitivity of rats on a protein-free diet to starvation). It is also apparent that high or low levels of dietary protein significantly reduce the time to death of diazinon-exposed rats. Clinical signs of diazinon intoxication were similar for all groups and included listlessness, fur soiling, hunched back, piloerection, prostration, exophthalmos, tremors/trembling, dacryorrhea, and shallow respiration (Boyd et al. 1969). A similar study was conducted in male Wistar rats in which the rats were fed defined diets varying in protein content (0, 3.5, 9, 26, and 81% vitamin-free casein) for 28 days prior to exposure to single doses of diazinon in oil by gavage. For rats fed the “normal” 26% casein diet (previously shown to be about equivalent to standard Purina lab chow), the LD₅₀ was determined to be 415 mg/kg for a single acute-duration oral exposure. The authors reported observing typical signs of cholinergic stimulation, followed by central nervous system depression. Few signs of protein deficiency were observed when the dietary protein was reduced to 9%, one-third the normal amount. However, diazinon toxicity was increased (i.e., the LD₅₀ was reduced) by a factor of 1.8. Even when the protein content was reduced to 3% and signs of protein deficiency were more marked, the LD₅₀ for diazinon was reduced by a factor of 1.9. However, rats fed the 0% protein (but normal caloric content) slowly lost body weight, became docile and hypothermic, and with declining water intake increasingly manifested oliguria, aciduria, and occasionally glycosuria. These rats were substantially more susceptible to diazinon toxicity, the LD₅₀

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being reduced 7.4-fold. Rats fed 8 1% casein demonstrated various signs of casein intoxication, and the diazinon LD₅₀ was reduced by a factor of 2.

Treatment of test animals with anticholinesterase agents such as atropine and 2-PAM significantly reduced the acute lethality of diazinon in rats indicating that acute diazinon lethality is primarily attributable to the inhibition of acetylcholinesterase. Administration of 16 mg/kg atropine intramuscularly, with or without 30 mg/kg pyridine 2-aldoxime methochloride (2-PAM) given either orally or intravenously or both, to female albino rats 10 minutes before diazinon exposure increased the LD₅₀ value (294 mg/kg) for diazinon for this species by a factor of 3.2 (with 2-PAM) or 1.7 (without 2-PAM) (Harris et al. 1969).

Deaths have been reported after oral exposure to diazinon in other acute-duration studies. Among Sprague-Dawley rats (10-15 of each sex) receiving a single oral gavage dose in corn oil of diazinon of 528 mg/kg, 2 of 15 males and 1 of 15 females died (Chow and Richter 1994). No deaths were reported at 2.2, 132, or 264 mg/kg diazinon. Six of 8 New Zealand rabbit dams died when given 30 mg/kg/day diazinon in capsules during gestation days 6-15 (Robens 1969), as did 9 of 22 in the same species receiving 100 mg/kg/day diazinon by gavage during gestation days 6-18 (Harris 1981). No deaths were reported at 7 mg/kg/day during gestation days 6-15 (Robens 1969), or at 7 and 25 mg/kg/day during gestation days 6-18 (Harris 1981) in New Zealand rabbits. No deaths were reported in pregnant CD-1 rats receiving 10, 20, or 100 mg/kg/day diazinon during gestation days 6-15 (Infurna et al. 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 males and 3 females per group) resulted in mortality (1 of 3 males and 1 of 3 females at 20 mg/kg). 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). In another study in which Hormel-Hanford miniature swine of both sexes were administered daily oral doses of diazinon dissolved in oil in capsules for up to 8 months resulted in mortality (100% in males and 67% in females) in 12-38 days of treatment at the highest dose tested (10 mg/kg/day) (Earl et al. 1971).

No deaths were reported in Sprague-Dawley rats (groups of 10 of each sex) receiving up to 183.2 mg/kg/day diazinon in feed for 6 weeks or up to 212 mg/kg/day (groups of 15 of each sex) for

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13 weeks (Singh 1988) or in Beagle dogs (groups of 4 of each sex) receiving up to 15.99 mg/kg/day in feed for 4 weeks or up to 11.6 mg/kg/day diazinon for 13 weeks (Barnes 1988). Survival rates were similar to controls in Sprague-Dawley rats receiving up to 12 mg/kg/day diazinon in feed for 98 weeks (Kirchner et al. 1991).

The LD₅₀ values and doses associated with death in each species and duration category are shown in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

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

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

Respiratory Effects. Respiratory distress, as a component of the spectrum of the symptoms of cholinergic reaction resulting from acetylcholinesterase inhibition, was reported in several human acute poisoning incidents and laboratory animal evaluation 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

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

Key to figure ^a	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					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 (LD ₅₀)	Boyd and Carsky 1969
3	Rat (Wistar albino)	once (GO)				415 M (LD ₅₀)	Boyd et al. 1969
4	Rat (Sprague-Dawley)	once (GO)				528 (2/15 males and 1/15 females died)	Chow and Richter 1994
5	Rat (Wistar albino)	once (GW)				408 M (LD ₅₀ : emulsified solution) 293 M (LD ₅₀ : wettable paste)	Edson and Noakes 1960
6	Rat (white)	once (GO)				300 M (LD ₅₀)	Enan et al. 1982
7	Rat (Sherman)	once (GO)				108 M (LD ₅₀) 76 F (LD ₅₀)	Gaines 1960
8	Rat (Sherman)	once (GO)				250 M (LD ₅₀) 285 F (LD ₅₀)	Gaines 1969
9	Rat (albino)	once (GO)				294 F (LD ₅₀)	Harris et al. 1969

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

Key to figure ^a	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
10	Rat (Sprague-Dawley)	once (GW)				2000 M (3/3 died)	Takahashi et al. 1991
11	Rabbit (New Zealand)	Gd 6-18 once/d (G)				100 F (9/22 died)	Harris 1981
12	Rabbit (New Zealand)	Gd 5-15 1x/d (C)				30 F (6/8 died)	Robens 1969
13	Chicken (Red Heavy)	once (GO)				10.9 F (LD ₅₀)	Jenkins 1988
Systemic							
14	Human	once (IN)	Resp Cardio Hemato Metabolic	240 M 509 F		240 M (tachypnea, cyanosis) 509 F 240 M (bradycardia, tachycardia) 509 F 240 M (metabolic acidosis) 509 F	Klemmer et al. 1978
15	Human	once (IN)	Resp Gastro			293 F (heavily congested lungs) 293 F (petechial hemorrhages throughout the stomach and gastric mucosa)	Poklis et al. 1980

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

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
16	Rat (Sprague- Dawley)	once (GO)	Hemato	528			Chow and Richter 1994
			Ocular Bd Wt		528 (chromodacryorrhea)	264 M (25% decrease in weight gain)	
17	Rat (Wistar)	7 d ad lib (F)	Bd Wt	0.21			Davies and Holub 1980b
18	Rat (CD-1)	Gd 6-15 once/d (G)	Bd Wt	20 F	100 F (5.5-9.6% decrease in maternal weight, 26-30% decrease in feed consumption)		Infuma et al. 1985
19	Rat (Sprague- Dawley)	once (GW)	Hemato		4.4 M (reduced platelet count, altered coagulation factor activities)		Lox 1983
20	Rat (Sprague- Dawley)	14 d ad libitum (W)	Hemato		52 F (reduced hematocrit, altered clotting factor activities)		Lox 1987
			Bd Wt	52			
21	Rat (Sprague- Dawley)	once (G)	Hepatic		300 (reduced hepatic cytochrome P-450, aniline hydroxylase, aminopyrine N-demethylase)		Mihara et al. 1981

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

Key to figure ^a	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
22	Rabbit (New Zealand)	Gd 6-18 once/d (G)	Resp	100 F			Harris 1981
			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			
23	Chicken (Red Heavy)	2x days 0, 21 (GO)	Bd Wt	11.3 F			Jenkins 1988
Neurological							
24	Human	once (IN)				240 M (stupor, profuse diaphoresis, coma) 509 F	Klemmer et al. 1978
25	Human	once (IN)				293 F (petechial hemorrhages throughout the brain)	Poklis et al. 1980
26	Rat (Sprague-Dawley)	once (GO)		2.2		132 (82% decrease in erythrocyte AChE, ataxia, alterations in functional observation battery tests 9-11 hrs post-dosing)	Chow and Richter 1994
27	Rat (Wistar)	7 d ad lib (F)		0.21			Davies and Holub 1980b

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

Key to figure ^a	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
28	Rat (Wistar albino)	once (GW)				300 M (erythrocyte AChE decreased 89% 24 hrs after exposure)	Edson and Noakes 1960
29	Rat (albino)	once (GO)				235 F (78% decrease in brain AChE)	Harris et al. 1969
30	Rat (Sprague-Dawley)	once (GW)		500 M		1000 M (fasciculations, twitches, convulsions, Straub tail reflex)	Takahashi et al. 1991
31	Hamster (Golden Syrian)	Gd 6, 7 and/or 8 1 x/d (GO)			0.125 F (diarrhea, salivation, incoordination)		Robens 1969
32	Rabbit (New Zealand)	Gd 6-18 once/d (G)		25 F		100 F (tremors, convulsion)	Harris 1981
33	Rabbit (New Zealand)	Gd 5-15 1 x/d (C)		7 F		30 F (ataxia)	Robens 1969
34	Chicken (Red Heavy)	2 x on days 0, 21 (GO)		11.3 F			Jenkins 1988
Reproductive							
35	Rat (CD-1)	Gd 6-15 once/d (G)		100 F			Infurna et al. 1985

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

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
36	Rabbit (New Zealand)	Gd 6-18 once/d (G)		100 F			Harris 1981
Developmental							
37	Rat (CD-1)	Gd 6-15 once/d (G)		20		100 (increased incidence of rudimentary ribs at T-14 in fetuses)	Infurna et al. 1985
38	Hamster (Golden Syrian)	Gd 6, 7 and/or 8 1 x/d (GO)		0.25			Robens 1969
39	Rabbit (New Zealand)	Gd 6-18 once/d (G)		100			Harris 1981
40	Rabbit (New Zealand)	Gd 5-15 1 x/d (C)		30			Robens 1969

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

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
INTERMEDIATE EXPOSURE								
Death								
41	Dog (Beagle)	8 mo 1 x/d (C)				10	(3/3 males and 2/3 females died)	Earl et al. 1971
42	Pig (Hormel- Hanford)	8 mo 1 x/d (C)				10	(3/3 males and 2/3 females died)	Earl et al. 1971
Systemic								
43	Rat (Wistar)	7-28 wk 2 x/wk (G)	Hepatic Bd Wt		0.5 M (lipid vacuolation) 0.5 M (10% reduction in body weight gain)			Anthony et al. 1986
44	Rat (Wistar)	35-92 d ad lib (F)	Bd Wt	1.35				Davies and Holub 1980a
45	Rat (Wistar)	30 d ad lib (F)	Bd Wt	2.86				Davies and Holub 1980b
46	Rat (Wistar albino)	16 wk ad lib (F)	Hepatic Renal Bd Wt	11.7 M 11.7 M 11.7 M				Edson and Noakes 1960

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

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
47	Rat (white)	4 wk ad lib (F)	Hepatic		30 M (reduced serum beta-lipoproteins, increased alanine aminotransferase, aspartate amino-transferase, gamma-glutamyl transferase, lactate		Enan et al. 1982
48	Rat (Sprague- Dawley)	6 mo ad lib (W)	Hemato	0.18 F			Lox and Davis 1983
			Hepatic	0.18 F			
			Bd Wt	0.18 F			

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

Key to ^a figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
49	Rat (Sprague- Dawley)	13 wk 7 d/wk ad lib (F)	Resp	168 M 212 F			Singh 1988
			Cardio	168 M 212 F			
			Gastro	19 M 15 F	168 M (soft stools) 212 F (soft stools)		
			Hemato	168 M 19 F		212 F (decreased hemoglobin and hematocrit; increase in reticulocytes)	
			Hepatic	168 M 19 F	212 F (increase in relative and absolute liver weight, minimal centrolobular hepatocellular hypertrophy)		
			Renal	168 M 212 F			
			Endocr	168 M 212 F			
			Ocular	168 M 212 F			
			Bd Wt	168 M 212 F			
			50	Rat (Sprague- Dawley)	6 wk 7 d/wk ad lib (F)	Gastro	
Bd Wt	8.4	150.8 M (15% decrease in body weight)					

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

Key to ^a figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
51	Dog (Beagle)	13 wk 7 d/wk (F)	Resp	11.6			Barnes et al. 1988
			Cardio	11.6			
			Gastro	11.6			
			Hemato	11.6			
			Hepatic	11.6			
			Renal	11.6			
			Endocr	5.6 M 11.6 F	10.9 M (atrophy of pancreatic acini)		
			Ocular	11.6			
			Bd Wt	5.9 M 0.21 F	10.9 M (34% decreased weight gain 5.6 F in males, 33% in females)		
			52	Dog (Beagle)	4 wk 7d/wk (F)	Hemato	
Hepatic	15.99						
Renal	15.99						
Bd Wt	0.8	14.68 M (weight loss)				15.99 F (emaciation-20% wt loss)	

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

Key to figure ^a	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
53	Dog (Beagle)	8 mo 1 x/d (C)	Cardio	5 M 20 F	10M (no pericardial fat, cord-like heart vessels)		Earl et al. 1971
			Gastro	5	10M (duodenal wall thickening)	20 (duodenal and stomach ruptures)	
			Hemato	10 F		10 M (peripheral anemia; bone marrow hypocellularity, increased myeloid element content, reticulocytopenia)	
			Hepatic	2.5	5 (markedly elevated serum aspartate aminotransferase and ornithine carbamyl transferase)	10 M (yellow, fatty liver; parenchymal atrophy, hepatocyte dissociation; moderate cirrhosis, focal necrosis, fibrous infiltration, elevated serum lactate dehydrogenase)	
			Renal	5 M 10 F		10 M (localized chronic nephritis, tubular atrophy, glomeruli with fibrous infiltration)	
			Endocr	5		10 M (pancreatic atrophy and interstitial fibrosis)	
			Bd Wt	5 M 10 F	10 M (significant weight loss) 20 F (significant weight loss)		

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

Key to figure ^a	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
54	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
			Hemato	2.5		5 (occasional transient peripheral anemia, reticulocytopenia, bone marrow hypocellularity, increased myeloid element content)	
			Hepatic		1.25 (slight inflammation, occasional lobular congestion)	2.5 (interlobular connective tissue thickening, degenerative hepatocytes, hepatic hemorrhage) 5	
Immunological/Lymphoreticular							
55	Rat (Sprague-Dawley)	13 wk 7 d/wk ad lib (F)		168 M 212 F			Singh 1988
56	Dog (Beagle)	13 wk 7 d/wk (F)		11.6			Barnes et al. 1988

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

Key to figure ^a	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Neurological							
57	Rat (Wistar)	35-92 d ad lib (F)		1.35			Davies and Holub 1980a
58	Rat (Wistar)	30 d ad lib (F)			2.86 (58% decrease in erythrocyte AChE)		Davies and Holub 1980b
59	Rat (Wistar albino)	16 wk ad lib (F)		0.44 M	2.26 M (46% decrease in erythrocyte AChE)	11.7 M (79% decrease in erythrocyte AChE)	Edson and Noakes 1960
60	Rat (Sprague-Dawley)	13 wk 7 d/wk ad lib (F)		0.4	15 M (27% decrease in erythrocyte AChE)		Singh 1988
61	Rat (Sprague-Dawley)	6 wk 7 d/wk (F)		0.2	8.4 M (21% decrease in erythrocyte AChE) 9.4 F (24% decrease in brain AChE)	150.8 M (58% decrease in brain AChE in males, 61% decrease in females) 183.2 F	Singh 1988
62	Dog (Beagle)	13 wk 7 d/wk (F)		0.021 ^b	5.9 (31% decrease in erythrocyte and brain AChE)		Barnes et al. 1988
63	Dog (Beagle)	4 wk 7 d/wk (F)		0.082	14.68 (30% decrease in erythrocyte AChE, 44% decrease in brain AChE, emesis)		Barnes et al. 1988

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

Key to figure ^a	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
64	Dog (Beagle)	8 mo 1 x/d (C)		5	10	(fasciculation, diarrhea, emesis)	Earl et al. 1971
65	Dog (mixed breed)	12 wk 7 d/wk (F)		0.019	1.9	(55% decrease in erythrocyte AChE)	Williams et al. 1959
66	Pig (Hormel-Hanford)	8 mo 1 x/d (C)		1.25	2.5	(emesis, diarrhea, fasciculations)	Earl et al. 1971
Reproductive							
67	Rat (Sprague-Dawley)	60 d ad libitum (F)		0.05			Green 1970
68	Rat (Sprague-Dawley)	13 wk 7 d/wk ad lib (F)		168 M 212 F			Singh 1988
69	Mouse (Hybrid)	Gd 1-18 1 x/d (F)			0.18	(14% reduced maternal weight gain, 20% reduced litter size)	Spyker and Avery 1977
70	Dog (Beagle)	13 wk 7 d/wk (F)		11.6			Barnes et al. 1988
71	Dog (Beagle)	8 mo 1 x/d (C)		5M		10 M (testicular atrophy, aspermatogenesis)	Earl et al. 1971

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

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Developmental								
72	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
73	Mouse (Hybrid)	Gd 1-18 1 x/d (F)				0.18	(neuromuscular coordination deficits, reduced litter size, delayed contact placing and sexual maturity)	Spyker and Avery 1977

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

Key to figure ^a	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
CHRONIC EXPOSURE							
Systemic							
74	Rat (Sprague-Dawley)	98 wks or 52 wks (F)	Resp	10 M 12 F			Kirchner et al. 1991
			Cardio	10 M 12 F			
			Gastro	10 M 12 F			
			Hemato	10 M 12 F			
			Musc/skel	10 M 12 F			
			Hepatic	10 M 12 F			
			Renal	10 M 12 F			
			Endocr	10 M 12 F			
			Dermal	10 M 12 F			
			Ocular	10 M 12 F			
			Bd Wt	10 M 12 F			
			Metabolic	10 M 12 F			

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

Key to figure ^a	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Immunological/Lymphoreticular							
75	Rat (Sprague-Dawley)	98 wks or 52 wks (F)		10 M 12 F			Kirchner et al. 1991
Neurological							
76	Rat (Sprague-Dawley)	98 wks or 52 wks (F)		0.06 M 0.07 F	5 M (24% decrease in brain AChE in males, 29% in females) 6 F		Kirchner et al. 1991
Reproductive							
77	Rat (Sprague-Dawley)	98 wks or 52 wks (F)		10 M 12 F			Kirchner et al. 1991

^aThe number corresponds to entries in Figure 2-2.

^bUsed to derive an intermediate-duration Minimal Risk Level (MRL) of 0.0002 mg/kg/day based on the NOAEL of 0.021 mg/kg/day for brain acetylcholinesterase inhibition, using an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

AChE = acetylcholinesterase; ad lib = ad libitum; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; gen = generation; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; (IN) = ingestion; LD₅₀ = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; Resp = respiratory; (W) = water; wk = week(s); x = times

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

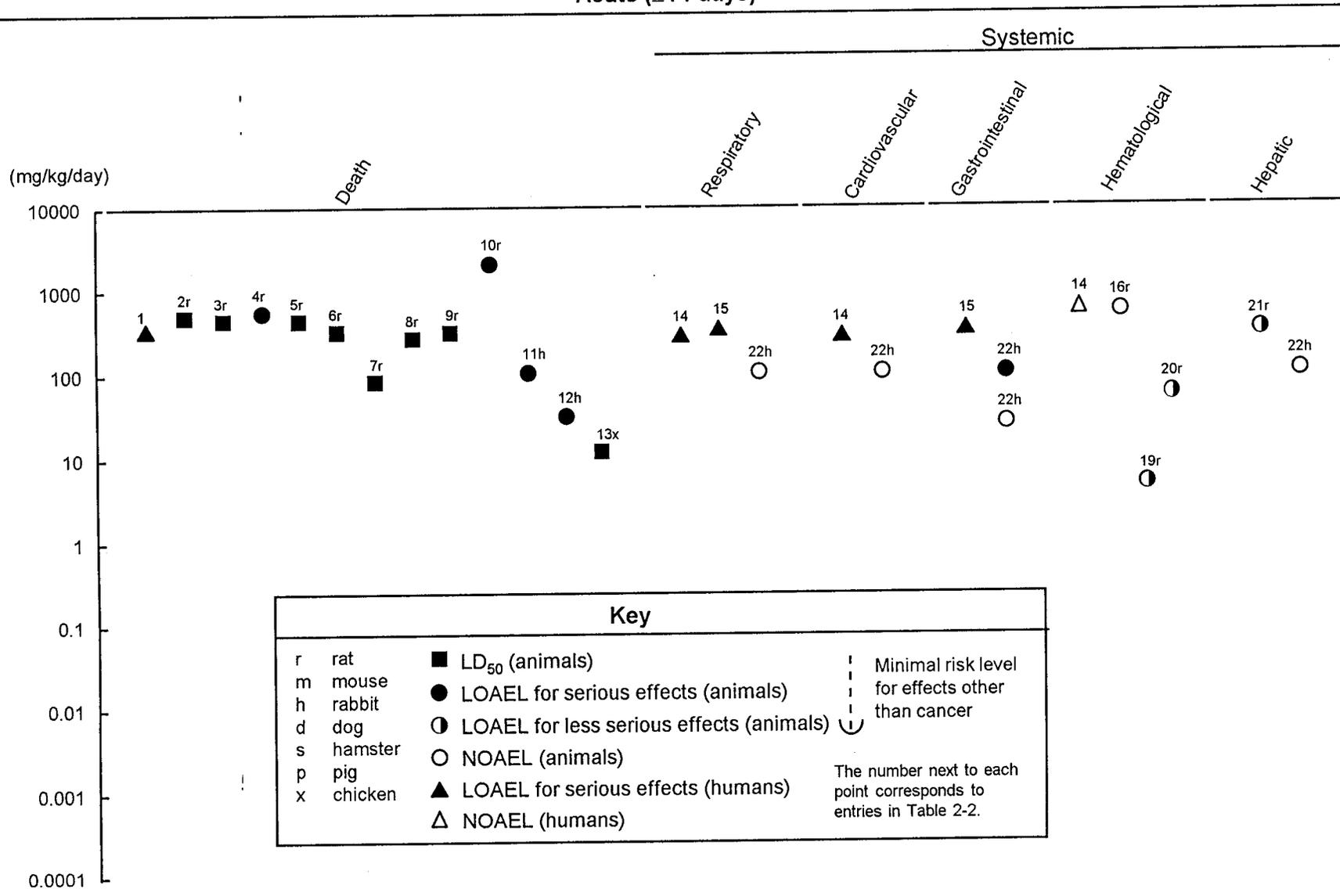


Figure 2-2. Levels of Significant Exposure to Diazinon - Oral (cont.)

Acute (≤ 14 days)

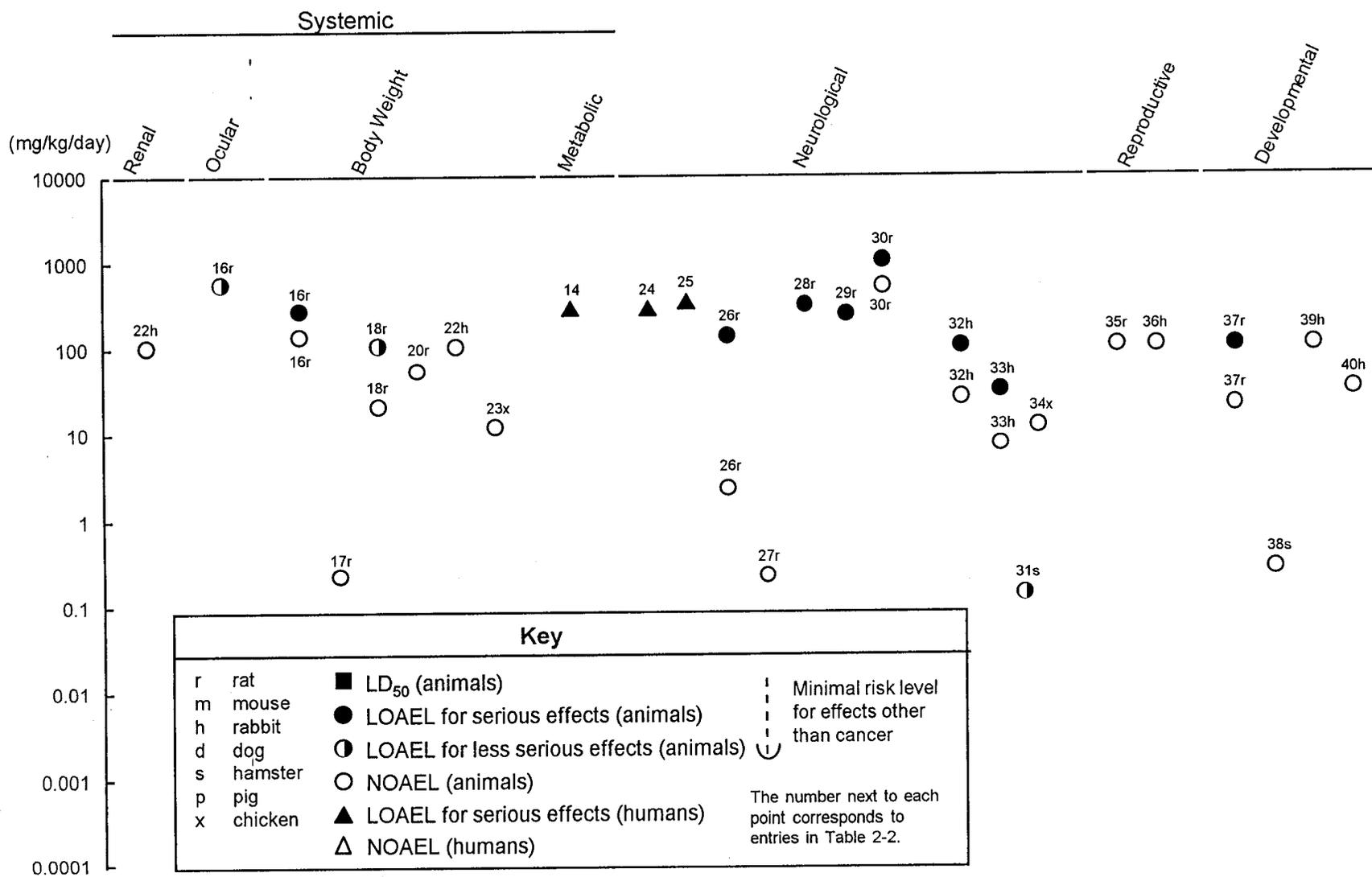


Figure 2-2. Levels of Significant Exposure to Diazinon - Oral (cont.)

Intermediate (15-364 days)

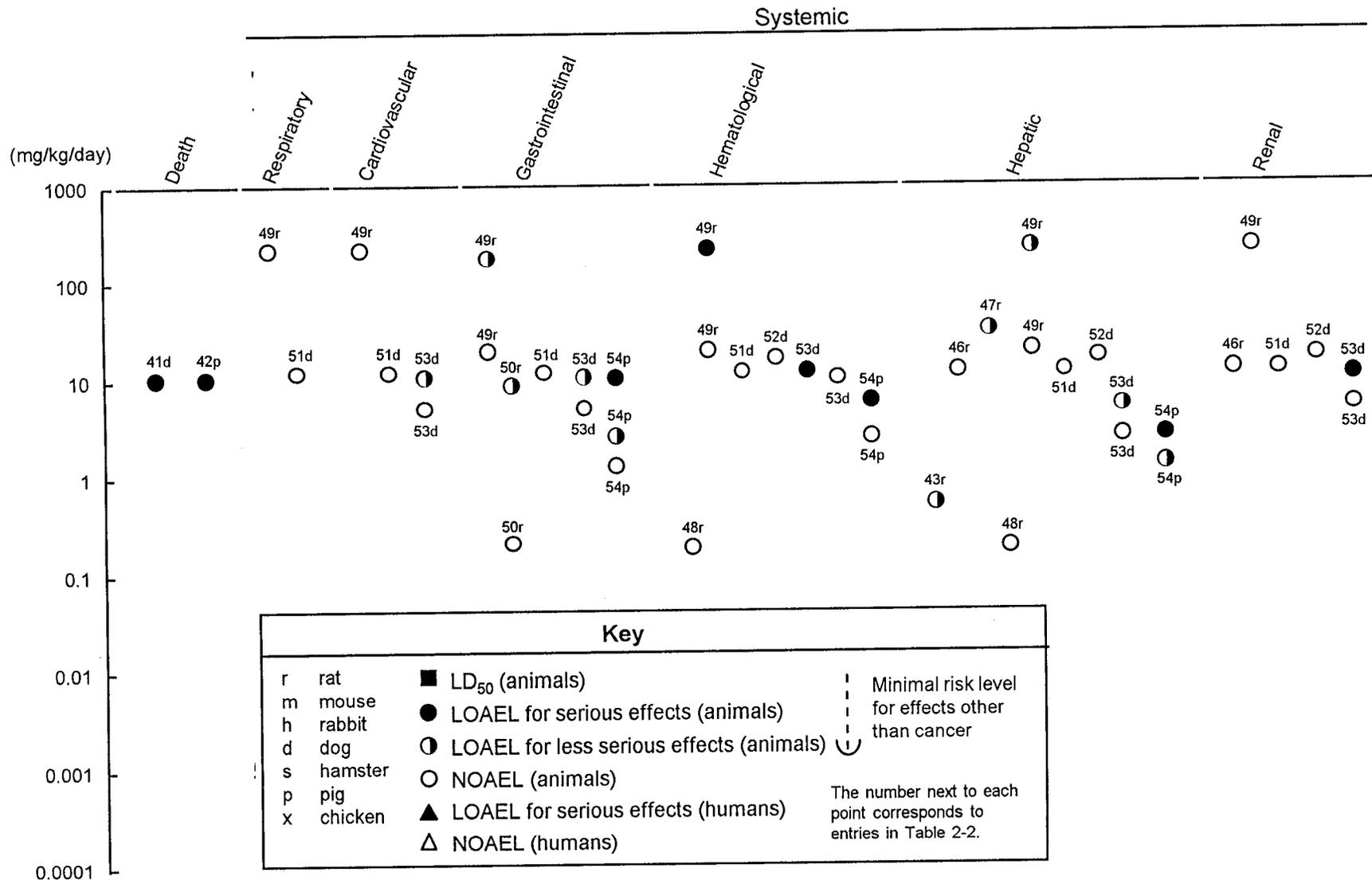


Figure 2-2. Levels of Significant Exposure to Diazinon - Oral (cont.)
Intermediate (15-364 days)

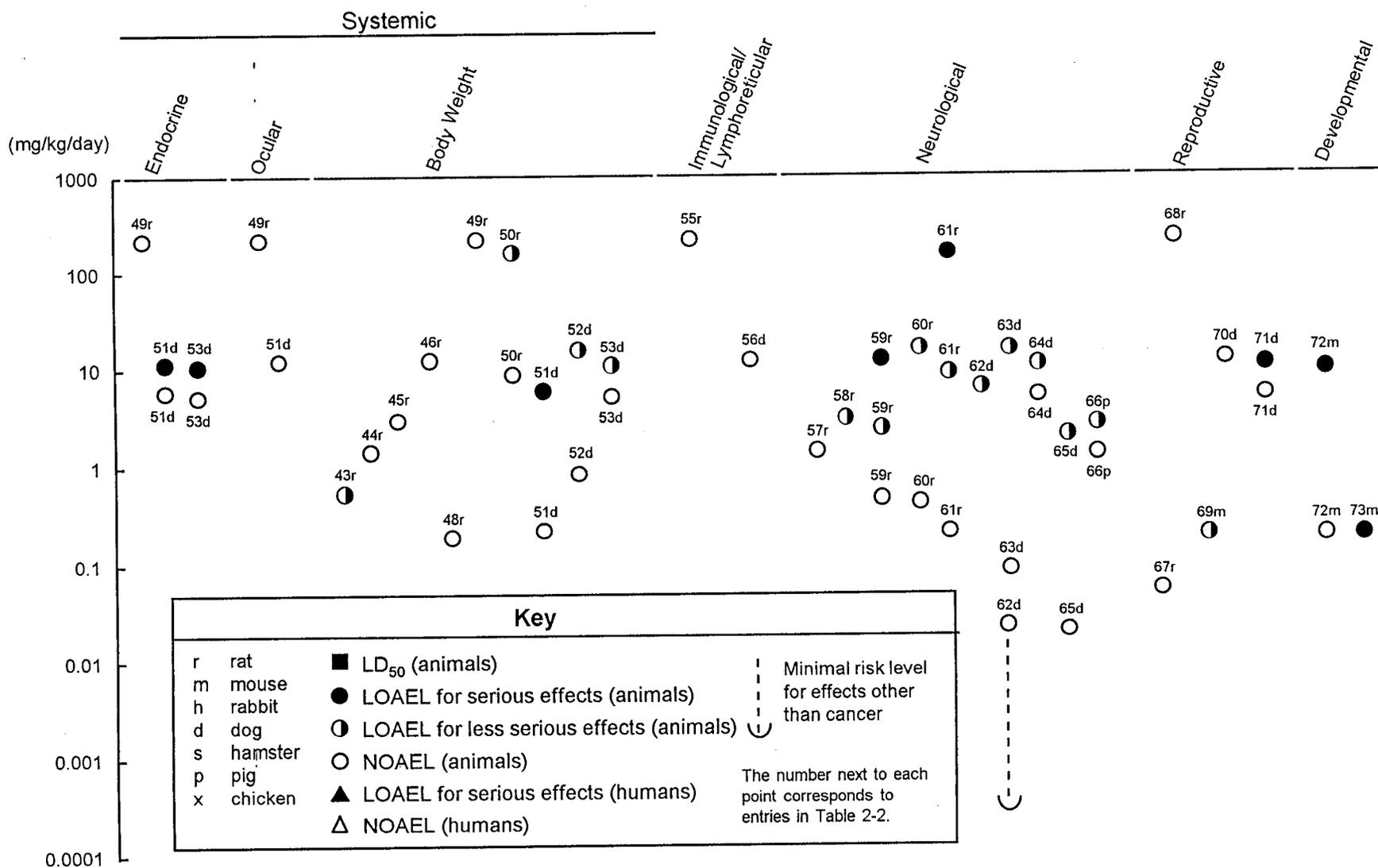
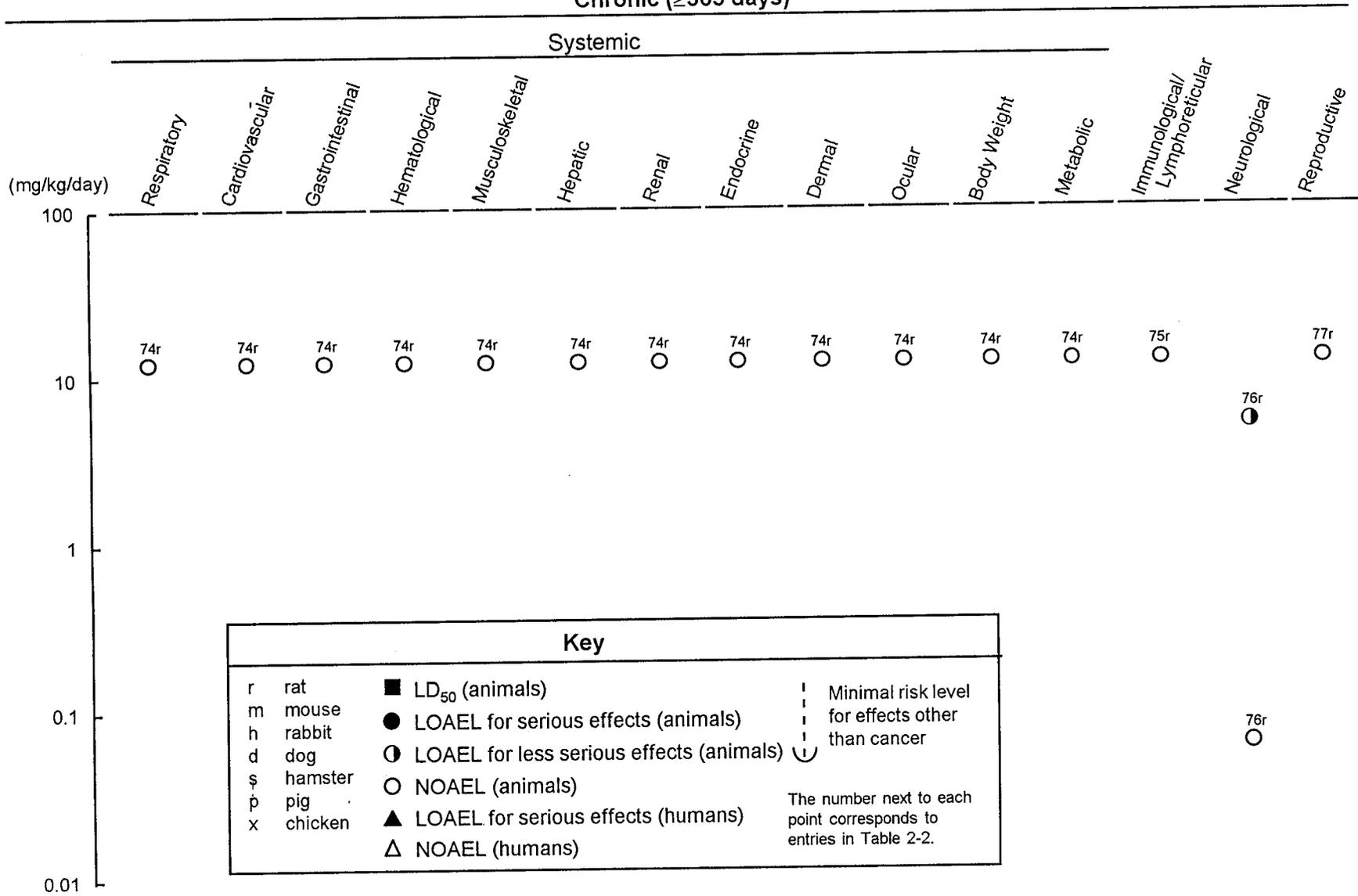


Figure 2-2. Levels of Significant Exposure to Diazinon - Oral (cont.)

Chronic (≥ 365 days)



2. HEALTH EFFECTS

50-700 mg/kg to rats resulted in respiratory distress from pulmonary inflammation, vascular congestion, venous stasis, and occasional extensive pneumonitis in the treated rats. 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 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 1981), in Sprague-Dawley rats (groups of 15 of each sex) 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 (groups of 4 of each sex) receiving up to 11.6 mg/kg/day diazinon for 13 weeks (Barnes 1988).

Cardiovascular Effects. Acute-duration oral, lethal human exposure to diazinon resulted in extensive congestion of the heart and blood vessels as reported in a summary of autopsy findings of 76 cases of acute diazinon poisoning which described cardiovascular signs that included: livid, congested face; soft flabby heart with conspicuous vasculature on the pericardium and epicardium; occasional and scattered petechial/ecchymotic hemorrhage; and cloudy swelling and hyperemia (upon histopathological examination) (Limaye 1966). In a case study of 25 persons that attempted suicide by ingesting diazinon, 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).

2. HEALTH EFFECTS

No gross or histological evidence of treatment-related damage to the heart 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 1981), in Sprague-Dawley rats (groups of 1.5 of each sex) 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 Beagle dogs (groups of 4 of each sex) receiving up to 11.6 mg/kg/day diazinon for 13 weeks (Barnes 1988).

Gastrointestinal Effects. A summary of autopsy findings of 76 cases of acute diazinon poisoning described gastrointestinal signs that include: dark, blood-stained stomach contents; congested stomach mucosa with submucosal petechial hemorrhage; and occasional erosion and ulceration (Limaye 1966). Petechial hemorrhages throughout the stomach and gastric mucosa were revealed in the autopsy report of a diazinon-poisoned 54-year-old female suicide victim who had ingested an estimated 293 mg/kg diazinon (Poklis et al. 1980). Other signs of gastrointestinal toxicity seen in humans after acute exposure to high doses of diazinon include nausea, diarrhea and vomiting (Balani et al. 1968; Klemmer et al. 1978), and abdominal pain (Balani et al. 1968). A 16-year-old female who drank an estimated 1.5 mg/kg of a diazinon formulation (Tik-20) developed pancreatitis after being treated for cholinergic manifestations. The pancreatic effects may well have been secondary to the diazinon-induced cholinergic manifestations (Dagli et al. 1981). Acute pancreatitis was also found in two children poisoned with diazinon (Weizman and Sofer 1992).

In male albino Wistar rats exposed to high acute doses of diazinon prior to death, 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 doses of diazinon for 8 months. Marked edematous thickening of the intestinal wall was observed in 5 of 6 dogs at the 20 mg/kg/day dose with one developing a duodenal rupture and subsequent peritonitis, and another a rupture of the pyloric portion of the stomach. At the 10 mg/kg/day dose, the duodenal wall thickening was observed only in the 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

2. HEALTH EFFECTS

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). Intermediate-duration treatment of Hormel-Hanford miniature pigs with daily doses of 1.25-10 mg/kg/day for 8 months resulted in injury to the gastrointestinal tract. At 10 mg/kg/day, 4 of 5 pigs which died had edematous thickening of the walls of the jejunum, 3 of 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 doses displayed edema of the jejunum, with serosal seepage of the ileum also observed 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. Abdominal ascites that clotted on exposure to air was reported without further description for one pig exposed to 2.5 mg/kg/day. This animal also suffered intestinal edema and serosal seepage, liver toxicity, and death on day 141 (Earl et al. 1971).

Stomach mucosal hemorrhage, congestion, and erosion were observed in 7 of 9 New Zealand rabbit dams that died while receiving 100 mg/kg/day diazinon during gestation days 6-18 (Harris 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 in 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 in 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 in feed for 4 weeks (Barnes 1988). Emesis, bloody feces, and diarrhea were observed in Beagle dogs receiving up to 11.6 mg/kg/day diazinon in feed for 13 weeks. These signs were not dose-related and were considered by the authors to be unrelated to treatment (Barnes 1988).

No histological evidence of treatment-related damage to gastrointestinal tissues was found in Sprague-Dawley rats receiving up to 12 mg/kg/day 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).

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Hematological Effects. A report on 5 individuals (3 males, 2 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).

In laboratory animal studies, the hematological effects of a single oral dose of 4.4 mg/kg diazinon was studied in Sprague-Dawley rats 2 hours after treatment. While 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 (< 0.05) changes were observed in activities of the remaining clotting factors; fibrinogen activity was reduced, while prothrombin, partial thromboplastin, factor II, factor V, and factor X activities were increased. Since fibrinogen and factors II, V, VII, and X are synthesized in the liver, the associated alterations may reflect hepatic effects of diazinon exposure. The data indicate an overall diazinon-induced condition of hyper coagulability that, considered together with observations from other studies of various haemorrhagia, may suggest that diazinon might affect hemostasis in general (Lox 1983). Other rats were exposed for 14 days to 52 mg/kg/day diazinon in drinking water and monitored for hematocrit and platelet count, and various clotting factor times were monitored (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 hyper coagulability 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 exposed to a lower dose of approximately 0.18 mg/kg/day diazinon in 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 Davies 1983). In another study, one dog treated with 20 mg/kg/day diazinon showed marked reductions in peripheral red blood cells, hematocrit, and hemoglobin. Its myeloid/erythroid (M/E) bone marrow ratio was evidently within the normal range. At the 20 mg/kg/day dose, all the dogs displayed greatly elevated M/E ratios (114-1 83/l as opposed to 1.1-1.9/l for controls) with slight to moderate bone marrow hypocellularity, and a pronounced

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reticulocytopenia in 2 dogs (one male, one female) (Earl et al. 1971). Intermediate-duration treatment of Hormel-Hanford miniature pigs with daily doses of diazinon resulted in hematological effects. Three of 6 pigs exposed to 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 5 pigs in the 10 mg/kg/day group, but all the pigs exhibited reticulocytopenia, with 3 displaying elevated M/E ratios (Earl et al. 1971).

Hematological parameters were normal in Sprague-Dawley rats (groups of 10-15 of each sex) 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 in 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 (groups of 4 of each sex) receiving up to 11.6 mg/kg/day diazinon in feed (Barnes 1988), or in Sprague-Dawley rats receiving up to 12 mg/kg/day for 98 weeks (Kirchner et al. 1991).

Hepatic Effects. A summary of autopsy reports of 76 human diazinon poisonings reported 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 in 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 betalipoprotein, 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

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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 (20 rats with 24 unexposed controls) 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 an intermediate-duration (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 for 8 months included slight inflammation and occasional lobular congestion with degenerative hepatocytes (Earl et al. 1971). Animals treated with a daily dose of 2.5 mg/kg exhibited interlobular connective tissue thickening and lobular congestion. In addition to the noted hepatic effects, all livers from swine exposed to 10 mg/kg/day were very firm to the touch and hard to cut, and one liver from a pig treated with 5 mg/kg/day diazinon was described as “friable” and very gritty, with focal subscapular hemorrhages.

An increase in relative and absolute liver weight was observed in female Sprague-Dawley rats receiving 212 mg/kg/day diazinon in feed for 13 weeks (Singh 1988). This was accompanied by histological evidence of minimal centrilobular hepatocellular hypertrophy. These findings were not seen in male rats receiving 168 mg/kg/day or females receiving 19 mg/kg/day or less. Relative liver weight was unchanged compared to controls in groups of 10 male Wistar rats receiving up to 11.7 mg/kg/day diazinon in feed for 16 weeks (Edson and Noakes 1960).

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 for 98 weeks (Kirchner et al. 1991), in New Zealand rabbit dams receiving up to 100 mg/kg/day diazinon during gestation days 618 (Harris 1981), or in Beagle dogs (groups of 4 of each sex) receiving up to 11.6 mg/kg/day diazinon for 13 weeks (Barnes 1988).

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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).

Relative kidney weight was unchanged compared to controls in groups of 10 male Wistar rats receiving up to 11.7 mg/kg/day diazinon in feed for 16 weeks (Edson and Noakes 1960). 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 618 (Harris 1981), in Sprague-Dawley rats (groups of 15 of each sex) 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 (groups of 4 of each sex) receiving up to 11.6 mg/kg/day diazinon for 13 weeks (Barnes 1988).

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. The concentration of diazinon in the liquid was not reported so a dose could not be calculated. 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 in feed for

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13 weeks (Barnes 1988). This effect was not observed in female Beagle dogs receiving 11.6 mg/kg/day in this study.

No gross or histological evidence of treatment-related damage to the adrenals after oral exposure to diazinon was observed in Sprague-Dawley rats (groups of 15 of each sex) receiving up to 212 mg/kg/day diazinon in 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 for 98 weeks (Kirchner et al. 1991), or in Beagle dogs (groups of 4 of each sex) 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 in feed for 13 weeks (Singh 1988), or up to 12 mg/kg/day for 98 weeks (Kirchner et al. 1991); and in Beagle dogs receiving up to 11.6 mg/kg/day diazinon in feed for 13 weeks (Barnes 1988).

Body Weight Effects. Dogs administered diazinon by the oral route in an intermediate-duration study exhibited significant weight loss at doses greater than 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 with daily oral dose of 0.5 mg/kg twice a week for 28 weeks. Body weight was significantly greater in 2% 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).

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 (Infuma et al. 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

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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 in feed had a 15% decrease in body weight compared to controls after 6 weeks (Singh 1988). Weight gain in females was unaffected. Significantly reduced rates of body weight gain were observed in male Beagle dogs receiving 10.9 mg/kg/day diazinon in feed (34%) and in females receiving 5.6 mg/kg/day (33%) for 13 weeks (Barnes 1988). Emaciation was observed in female Beagle dogs receiving 15.99 mg/kg/day diazinon in feed for 4 weeks. Less severe, but still significant, weight loss was observed in male Beagle dogs receiving 14.68 mg/kg/day (Barnes 1988).

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 1981). In studies with rats, no effect on body weight was observed in female Wistar rats receiving up to 1.35 mg/kg/day in feed for 92 days (Davies and Holub 1980a); in male Wistar rats receiving up to 11.7 mg/kg/day in feed for 16 weeks (Edson and Noakes 1960); in Wistar rats of both sexes receiving 0.21 mg/kg/day in 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 in feed for 13 weeks (Singh 1988), 0.18 mg/kg/day in drinking water for 6 months (Lox and Davies 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), or in chickens receiving 2 doses of 11.3 mg/kg diazinon by gavage 21 days apart and observed for a further 21 days (Jenkins 1988).

Metabolic Effect. 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 for 98 weeks (Kirchner et al. 1991).

2.2.2.3 Immunological and Lymphoreticular Effects

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

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In laboratory animal studies, 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. Diazinon treatment also reduced thymus weight and resulted in thymic atrophy ranging from minor to near total loss of thymocytes (Boyd and Carsky 1969). One Beagle dog in the 10 mg/kg/day dose group in an intermediate-duration study in which groups of dogs were administered oral doses of 2.5-20 mg/kg/day diazinon exhibited splenic atrophy prior to death. The spleen of an anorexic and emaciated male dog given to 10 mg/kg/day diazinon was markedly shrunken and pale in appearance with moderate atrophy in the splenic pulp prior to death after 232 days of exposure (Earl et al. 1971). The splenic atrophy reported in this study may be a result of the generalized emaciated condition of the dog due to diarrhea, emesis, and anorexia, as reported in the study.

No gross or histological evidence of treatment-related damage to the spleen or thymus after oral exposure to diazinon was observed in Sprague-Dawley rats (groups of 15 of each sex) 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 (groups of 4 of each sex) receiving up to 11.6 mg/kg/day diazinon for 13 weeks (Barnes 1988).

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

2.2.2.4 Neurological Effects

Diazinon, an anticholinesterase organophosphate, exerts its action by inhibiting neural acetylcholinesterase in the central and peripheral nervous system. Diazinon itself is a poor inhibitor of acetylcholinesterase, but is converted by mixed-function oxygenases in the liver to its oxon form, diazoxon. Diazoxon also inhibits acetylcholinesterase and is much more potent than diazinon. The extent to which this reaction takes place has a significant effect on toxicity. This inhibition results in the accumulation of -acetylcholine at acetylcholine receptors leading to muscarinic and nicotinic effects in the peripheral nervous system and central nervous system effects. These effects usually appear within a few minutes to 24 hours after dosing, depending on the extent of exposure. Signs and symptoms of diazinon-induced cholinergic effects are manifested in humans following exposure. Similarly, animals exhibit signs of diazinon cholinergic toxicity. Recovery from diazinon poisoning

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results from increased availability of active acetylcholinesterase either from synthesis of new enzyme or the spontaneous hydrolysis of the enzyme-phosphate ester complex.

Acetylcholinesterase activity is also present in erythrocytes where it is known as erythrocyte acetylcholinesterase. Both forms of acetylcholinesterase are produced by the same gene and are kinetically identical (Taylor et al. 1993). In *in vitro* assays, erythrocyte and neural acetylcholinesterase are inhibited to roughly the same extent by exposure to diazinon and many other organophosphorus compounds with insecticidal activity (Iyaniwura 1991); measurement of erythrocyte acetylcholinesterase can be used as a surrogate indicator of the extent of inhibition of neural acetylcholinesterase. A cholinesterase capable of hydrolyzing acetylcholine and butyrylcholine is produced by the liver and circulates in the blood. This enzyme, referred to as serum cholinesterase or butyrylcholinesterase, is also inhibited by diazinon and is often used as a marker for exposure. The *in vivo* substrate of this enzyme is unknown. In general, this enzyme is inhibited by diazinon at lower levels of exposure than required to inhibit neural or erythrocyte acetylcholinesterase (Barnes 1988; Singh 1988).

Signs and symptoms of cholinergic poisoning are usually seen in diazinon poisoning. In a case study of 25 persons who attempted suicide by ingesting diazinon, the most commonly reported symptom was vomiting followed by unconsciousness, giddiness, excessive sweating, and diarrhea. Clinical examinations revealed tachycardia and constricted pupils in many of the patients while some patients also became drowsy and then comatose (Kabrawala et al. 1965). A summary of autopsy findings of 76 cases of acute diazinon poisoning described signs that included congested, swollen, edematous brain with prominent dural and surface vasculature; and occasional brain hemorrhage or spinal hemorrhage (Limaye 1966). Following a suicide attempt by a woman who ingested a large quantity of diazinon, cholinergic signs were evident such as pin-point pupils and muscle fasciculation. A neurological examination showed lateral nystagmus and gross incoordination. Immediately after treatment, although the patient recovered from the acute effect, she was unable to walk or hold objects. The patient recovered within one week (Bichile et al. 1983). A report on 5 individuals (3 male, 2 female) 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) described cholinergic signs and symptoms that included bradycardia, tachycardia, clonus, stupor, profuse diaphoresis, sialorrhea, miosis, hyperreflexia, weakness, dysdiadokinesis, abdominal pain, nausea, coma, twitching, restlessness, hyperreflexia, and bronchospasm. Many, but not all, of the listed effects were observed at one or

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more time points in each of the five cases. In some cases, initial and treatment-concurrent measurements of serum and red blood cell cholinesterase activities indicated significant reduction. The victims responded well to atropine and 2-PAM treatment (Klemmer et al. 1978). Another report described an incident involving 100 persons (55 males, 45 females), most or all of whom attempted suicide by drinking diazinon formulation known as Tik-20 in India. Cases were graded according to severity of symptoms: Grade I, no clinical signs (14); Grade II, only symptoms including vomiting, diarrhea, abdominal pain, giddiness (21); Grade III, miosis with or without Grade II symptoms (27); Grade IV, pulmonary edema, with or without Grade II/III symptoms (23); and Grade V, unconsciousness, with or without Grades II-IV symptoms (15) (Balani et al. 1968). In another report of Tik-20 poisoning in India, a 16-year-old female who ingested 1.5 mg/kg diazinon (by drinking 10 mL of Tik-20) developed cholinergic signs and symptoms which included nausea, epigastric pain, headache, miosis and unreactive pupils, and tachycardia. All symptoms resolved within several hours following treatment with atropine and 2-PAM (Dagli et al. 1981). Many other studies have reported acute poisoning of persons resulting from ingestion of diazinon (Hata et al. 1986; Reichert et al. 1977; Wadia et al. 1974; Wedin et al. 1984). Other neurological effects reported in humans include petechial hemorrhages throughout the brain at autopsy in the case of a woman who ingested 293 mg/kg diazinon (Poklis et al. 1980).

In laboratory animal studies, a single oral administration of 50-700 mg/kg diazinon to albino Wistar rats resulted in signs of nervous system toxicity that included diarrhea, sialorrhea, dacryorrhea, ataxia, epistaxis, tachypnea, exophthalmos, tremors, anorexia, listlessness, diuresis, dyspnea, prostration, and hypothermia. These signs were reversible in animals which survive. Use of a low purified-protein diet did not significantly affect these signs (Boyd and Carsky 1969). Male Sprague-Dawley rats given a single oral dose of 500 mg/kg diazinon showed no abnormal clinical signs during the 48-hour period after exposure. Conversely, fasciculations, twitches, convulsions, lacrimation, chromodacryorrhea, exophthalmos, gasping, salivation, prostration, urination, and Straub tail reflex were observed in rats given a single oral dose of 1,000 mg/kg diazinon (Takahashi et al. 1991). A single 2,000 mg/kg dose resulted in substantial reductions in cholinesterase activities: in brain, 80-85%; in erythrocytes, 90%; and in serum, 50-55%. Cholinesterase activity was monitored in serum and erythrocytes of male Wistar rats 2 hours, 24 hours, 4 days, and 7 days after oral exposure to 300 mg/kg diazinon, and in the brain after 7 days (Edson and Noakes 1960). Expressed as reduction from control activity, the resulting time-course values were 42, 2, 19, and 0% (serum); 26, 89, 44, and 28% (erythrocytes); and 26% (brain). Diazinon exhibited very slow, but eventual, severe depression of red blood cell

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cholinesterase activity, with only modest serum activity. Significant depression was observed at 7 days in red blood cells and brain, even though the animals had apparently clinically recovered (Edson and Noakes 1960). Albino rats were dosed once with diazinon in oil by gavage, some groups having subsequent treatment with 16 mg/kg atropine (intramuscular), with or without 30 mg/kg of pyridine 2-aldoxime methochloride given orally and/or intravenously. In rats exposed to 235 mg/kg diazinon ($0.8 LD_{50}$), reductions in cholinesterase activity relative to controls after 3 hours was approximately 77% in the diaphragm and 78% in the brain, and after 24 hours, 84 and 77%, respectively. By 140 hours after diazinon exposure, diaphragm activity had recovered to a 37% reduction while brain activity was still reduced by 55%. The effect of pyridine 2-aldoxime methochloride on reactivating diaphragm cholinesterase activity was examined by exposing rats to 235 mg/kg diazinon and 10 minutes later to 16 mg/kg atropine (to reduce lethality), followed 24 hours later with either oral or intravenous 30 mg/kg pyridine 2-aldoxime methochloride. One hour later, reductions in cholinesterase activity with respect to untreated controls were approximately 89% in diazinon animals, 65% in animals administered diazinon and oral pyridine 2-aldoxime methochloride, and 55% in animals administered diazinon and intravenous pyridine 2-aldoxime methochloride (Harris et al. 1969).

In an extensive study of the neurological effects of diazinon after a single oral dose (Chow and Richter 1994), groups of lo-15 Sprague-Dawley rats of both sexes were treated by gavage with doses of 2.2, 132, 264, or 528 mg/kg diazinon and observed in a functional observation battery (FOB) of tests as well as serum and erythrocyte acetylcholinesterase analysis at the expected time of peak effect (9-11 hours after dosing). FOB effects were seen only at the expected time of peak effect and not at weeks 1 or 2. Autonomic effects (with ratio affected at the lowest dose) included: altered fecal consistency (3 of 10 at 264 mg/kg), impaired respiration (6 of 10 at 528 mg/kg), lacrimation (5 of 10 at 528 mg/kg), soiled fur (3 of 10 at 264 mg/kg), stained nose (3 of 10 at 264 mg/kg), and repeated opening and closing of mouth (1 of 10 at 132 mg/kg). Neuromuscular effects noted in males included: ataxia (9 of 10 at 264 mg/kg), abnormal gait (2 of 10 at 132 mg/kg), impaired righting reflex (2 of 10 at 264 mg/kg) impaired hindlimb extensor reflex (3 of 10 at 264 mg/kg), reduced forelimb grip strength (3 of 10 at 528 mg/kg), and decreased hindlimb foot splay. Neuromuscular effects noted in females included: ataxia (3 of 10 at 132 mg/kg), abnormal gait (7 of 10 at 132 mg/kg), impaired righting reflex (2 of 10 at 264 mg/kg), impaired hindlimb extensor reflex (6 of 10 at 528 mg/kg), abnormal hindlimb positioning (3 of 10 at 528 mg/kg), and reduced forelimb and hindlimb grip strength (all at 528 mg/kg). Central nervous system activity effects consisted of decreased rearing in a

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2-minute period in males at or above 264 mg/kg, and in females at or above 132 mg/kg. Central nervous system excitability effects noted in males included tremors (1 of 10 at 264 mg/kg), body twitch (5 of 10 at 264 mg/kg), lowered arousal level (all at 528 mg/kg), and easier handling (528 mg/kg). Central nervous system excitability effects noted in females included tremors (5 of 10 at 264 mg/kg), body twitch (3 of 10 at 264 mg/kg), lowered arousal level (all at 264 mg/kg), and easier handling (all at 264 mg/kg). Sensorimotor effects consisted of reduced touch response in 3 of 10 females at 528 mg/kg, and decreased tail pinch response in both sexes at 528 mg/kg. Physiologic effects consisted of reduced touch response in 3 of 10 females at 528 mg/kg, and decreased tail pinch response in both sexes at 528 mg/kg. Figure-8 maze activity was significantly suppressed (76%) in males exposed to diazinon at doses of 264 mg/kg or more ($p < 0.01$). Likewise, maze activity was significantly suppressed (46%) in females exposed to diazinon at doses of 132 mg/kg or more ($p < 0.01$). Doses of 528 mg/kg resulted in 97.4 and 95% decreases in maze activity among males and females, respectively. Serum cholinesterase levels were significantly reduced (28 and 53%) at the expected time of peak effect in males and females at doses > 2.2 mg/kg. Erythrocyte acetylcholinesterase levels were also reduced (82%) at this time at diazinon levels > 132 mg/kg in both sexes. Brain acetylcholinesterase levels, measured only at day 15, were not affected by diazinon. No gross or histopathologic changes were detected in the brain, spinal cord, peripheral nerves, skeletal muscle, eyes, or optic nerve.

Cholinergic signs of diarrhea and excessive salivation were observed in pregnant Golden Syrian hamsters orally exposed to 0.125 mg/kg/day of diazinon during gestation days 6-8 (Robens 1969). In this same study pregnant New Zealand rabbits orally exposed to 30 mg/kg/day during gestation days 6-15 exhibited these signs plus ataxia; no cholinergic signs were observed in dams exposed to 7 mg/kg/day. In another study on pregnant New Zealand rabbits orally exposed to 7, 25, or 100 mg/kg/day diazinon over gestation days 6-18 (Harris 1981), tremors and convulsions were noted in the 100 mg/kg/day group, but no cholinergic signs in the 25 mg/kg/day group.

In intermediate-duration studies, male Wistar rats were given a single oral dose of 1.75 mg/kg diazinon in 50% ethanol in water by oral gavage twice a week to study its effect on several neurotransmitters (Rajendra et al. 1986). No significant changes were noted after 7 or 14 weeks, but after 28 weeks, serum (but not erythrocyte or brain) cholinesterase activity was significantly ($p < 0.05$) reduced by 49%, brain dopamine was significantly elevated by 274%, and brain gamma aminobutyric acid was reduced by 32%. The increase in brain dopamine content over control reported in this study is due to an

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unexplained decline in control dopamine levels (from 0.55 $\mu\text{g/g}$ at 7 weeks to 0.19 $\mu\text{g/g}$ at 28 weeks). No significant changes were observed for blood serotonin, or brain aspartate, glutamate, tam-me, or glutamine (Rajendra et al. 1986). Male Wistar rats were exposed for 16 weeks to diazinon equivalent to 0.1-11.7 mg/kg/day in their feed. At the end of the experiment, rats given 2.26 mg/kg or 11.7 mg/kg exhibited reduced serum cholinesterase activity by 17 and 52% respectively, and erythrocyte acetylcholinesterase by 46 and 79% respectively. None of these treatments produced clinical signs or changes in body weight gain, food intake, or relative liver and kidney weights (Edson and Noakes 1960). Male Wistar rats fed diazinon doses of 0 or 0.21 mg/kg/day for 7 days did not exhibit a significant reduction in serum cholinesterase or erythrocyte acetylcholinesterase activity, whereas, in female rats, serum cholinesterase activity was reduced by 29% as compared to that of untreated female controls (erythrocyte acetylcholinesterase activity was not significantly changed). These results indicate that female Wistar rats are more sensitive to diazinon toxicity than are males, and that serum cholinesterase is the more sensitive indicator of diazinon toxicity (Davies and Holub 1980b). Treatment of female Wistar rats with 0.45-1.35 mg/kg/day diazinon for 92 days, 0.09-0.36 mg/kg/day diazinon for 42 days and 0.009-0.18 mg/kg/day diazinon for 35 days in the feed also produced no visible toxic manifestations. Serum cholinesterase activity was a more sensitive indicator than erythrocyte acetylcholinesterase activity, while brain acetylcholinesterase activity was insensitive to these levels of diazinon. Maximum inhibition was achieved after 31-35 days of exposure. According to the authors, female rats were used in this study because of the greater sensitivity of females to dietary diazinon toxicity compared to males as determined in a previous study. The dose of 1.35 mg/kg/day, administered for 92 days, is considered a NOAEL for erythrocyte and brain acetylcholinesterase inhibition (Davies and Holub 1980a). In a subsequent study, Wistar rats of both sexes fed diazinon doses of 0 or 2.86 mg/kg/day for 30 days showed no clinical signs of toxicity. Diazinon treatment produced a significant depression of erythrocyte and brain acetylcholinesterase activity among treated rats at all sampling times. At all times, depression of erythrocyte acetylcholinesterase enzyme activity was greater in females than in males; at 21 days post-treatment, and continuing throughout the study, reduction of erythrocyte acetylcholinesterase activity among treated females was significantly greater (13-17%) than among treated males. Serum cholinesterase activity was reduced by 46% (males) and 69% (females) as compared to sex-paired controls by 30 days post-treatment. Erythrocyte acetylcholinesterase levels declined more gradually, reaching 30-day levels of 45% (male) and 58% (female) relative to sex-paired controls. On day 15 of treatment, brain acetylcholinesterase activity among diazinon-treated rats were not significantly different for female rats relative to sex-paired controls (5.82 $\mu\text{mol/g}$ tissue/minute in controls as

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compared to 5.65 $\mu\text{mol/g}$ tissue/minute in diazinon-treated animals). On day 30, brain acetylcholinesterase levels were reduced by 7% for female rats relative to sex-paired controls (6.31 $\mu\text{mol/g}$ tissue/minute in controls as compared to 5.89 $\mu\text{mol/g}$ tissue/minute in diazinon-treated animals). It was concluded that serum cholinesterase activity is the most sensitive measure of diazinon exposure, and that female Wistar rats are more sensitive than males (Davies and Holub 1980b).

Daily oral administration of 10 or 20 mg/kg/day diazinon for 8 months resulted in fasciculations, emesis, diarrhea, with or without loss of appetite in Beagles (Earl et al. 1971). In another dog study, mixed breed female and male dogs were given diazinon in the feed at an equivalent dose of 0.006, 0.019, or 1.9 mg/kg/day for 12 weeks. While the lowest dose had no significant effect on serum cholinesterase, the intermediate dose reduced its activity to 60-80% of control and the high dose resulted in 5-30% of control activity. Enzyme activity returned to normal after 2-6 weeks. Only the highest dose (1.9 mg/kg/day) significantly reduced erythrocyte acetylcholinesterase by 55% after 12 weeks of exposure. This level was still reduced 28% 6 weeks after cessation of exposure (Williams et al. 1959). Cholinergic signs were also evident in some Hormel-Hanford pigs that were orally treated for 8 months with diazinon in capsules. Toxicity signs appeared 3-26 days after beginning the highest dose of 10 mg/kg/day (Earl et al. 1971).

Neurological effects observed in Sprague-Dawley rats receiving 0.04, 0.2, 8.4, or 150.8 mg/kg/day diazinon in feed (males) and 0.05, 0.2, 9.4, or 183.2 (females) in feed for 6 weeks (Singh 1988) included statistically significant decreases in erythrocyte acetylcholinesterase at 24 days in males at 8.4 mg/kg/day (21%) and at 150.8 mg/kg/day (20%), and at 24 days in females at 9.4 mg/kg/day (21%) and 183.2 mg/kg/day (25%). Statistically significant decreases in brain acetylcholinesterase were seen in males at the termination of the study at 150.8 mg/kg/day (58%), and in females at 9.4 mg/kg/day (24%) and at 183.2 mg/kg/day (61%). No treatment-related effects were noted for absolute or relative brain weights. A 13-week study using similar doses (Singh 1988) reported treatment-related clinical symptoms including hypersensitivity to touch and sound in the 168 mg/kg males and 212 mg/kg females. Males in the 168 mg/kg dose group also exhibited aggressive behavior. At termination, hyperactivity was noted in the 168 mg/kg males and 212 mg/kg females. Statistically significant decreases were seen in erythrocyte acetylcholinesterase in males at 15.0 mg/kg/day (27%) and at 168 mg/kg/day (26%) and in females at 0.4 mg/kg/day (17%), 19 mg/kg/day (41%) and at 212 mg/kg/day (41%). Statistically significant decreases were seen in brain acetylcholinesterase in males at 168 mg/kg/day (49%), and in females at 19 mg/kg/day (41%) and 212 mg/kg/day (57%). No

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gross or histopathologic changes were detected in the brain, spinal cord, peripheral nerves, skeletal muscle, eyes, or optic nerve.

Beagle dogs receiving doses of 0.02, 0.073, 0.8, or 14.68 mg/kg/day diazinon in males and 0.023, 0.082, 0.75, or 15.99 mg/kg/day (females) in feed for 4 weeks (Barnes 1988) exhibited statistically significant decreases in erythrocyte acetylcholinesterase in males at 0.073 mg/kg/day (11%) and at 14.68 mg/kg/day (30%), and in females at 15.99 mg/kg/day (38%). Statistically significant decreases in brain acetylcholinesterase were seen in males at 14.68 mg/kg/day (44%) and in females at 15.99 mg/kg/day (50%). No treatment-related changes in absolute or relative brain weights were noted. In a 13-week study using similar doses (Barnes 1988) statistically significant reductions in erythrocyte and brain acetylcholinesterase levels were noted in males and females beginning at the 5.9 and 5.6 mg/kg levels respectively. No change was observed in blood drawn on day 12. On days 29, 56, and 86 erythrocyte acetylcholinesterase declined by 26, 25, and 25% in males and 31, 31, and 31% in females at these doses. Levels in the highest dose groups (10.9 and 11.6 mg/kg/day) were similar. Brain samples analyzed at the termination of the study showed reduction of acetylcholinesterase activity of 31% in males at 5.9 mg/kg/day and 42% at 10.9 mg/kg/day. Female brain acetylcholinesterase activity was reduced 30% at 5.6 mg/kg/day and 45% at 11.6 mg/kg/day. Clinical signs included emesis and diarrhea, but were not dose related. No pathology of any nervous tissues were noted under either gross or microscopic examination.

In a chronic-duration study in Sprague-Dawley rats, diazinon was administered in feed at doses of 0.004, 0.06, 5, or 10 mg/kg/day (males) and 0.005, 0.07, 6, or 12 mg/kg/day (females) for 52 or 98 weeks (Kirchner 1991). Clinical signs of organophosphate neurological toxicity (diarrhea, salivation, lacrimation, tremor, etc.) were not observed in any treated groups. After one year, erythrocyte acetylcholinesterase was decreased 16 and 11% at 5 and 10 mg/kg/day, respectively, in males and 22 and 20% at 6 and 12 mg/kg/day in females, respectively. During a subsequent 4-week recovery period, male erythrocyte acetylcholinesterase returned to normal, while that of females dosed at 12 mg/kg/day was still decreased by 7%. Results were similar at 98 weeks: decreases of 21 and 22% in males at 5 and 10 mg/kg/day, respectively, and decreases in females of 26 and 25% at 6 and 12 mg/kg/day, respectively. No statistically significant reduction in brain acetylcholinesterase was observed in males after 1 year; however, activity in females decreased by 26 and 40% at doses of 6 and 12 mg/kg/day, respectively. During a 4-week recovery period, brain acetylcholinesterase activity in the 12 mg/kg/day female group recovered from 40% to 9% inhibition. After 98 weeks, significant

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decreases in brain acetylcholinesterase activity were present in males. Decreases of 24 and 42% were observed in the 5 and 10 mg/kg/day groups, respectively. Female brain acetylcholinesterase inhibition at 98 weeks was similar to that seen after 1 year. Decreases of 29 and 48% were observed in the 6 and 12 mg/kg/day groups, respectively. No histopathologic evidence of treatment-related damage was observed in the brain, optic nerves, spinal cord, or sciatic nerve, at either 52 or 98 weeks.

Diazinon MG-8 (purity 87%) has been tested for organophosphate-induced delayed neurotoxicity in chickens (Jenkins 1988). Ten hens (Red Heavy breed) were used as a control group and received 1.0 mL/kg of corn oil by gavage on days 0 and 21 of the study. Eighteen hens received 11.3 mg/kg diazinon in 1.0 mL of corn oil by gavage on days 0 and 21 (the approximate LD₅₀ in hens for this chemical). A positive control group of 8 hens received 500 mg/kg of the known delayed neurotoxicant tri-*o*-tolyl phosphate. Pretreatment with atropine (10 mg/kg) one hour before dosing and treatment at dosing with 2-PAM (50 mg/kg) were used to protect against acute cholinergic effects in all groups. All hens were also treated with atropine and 2-PAM one and five hours after dosing. Two hens required and received protective treatment the following day. All hens were observed and scored independently for signs of delayed neurotoxicity (gait disturbances, ataxia) by two different observers three times weekly. By day 13, all the positive control hens showed some degree of neurotoxicity (unsteadiness in walking to marked staggering and falling). None of the diazinon-treated hens displayed these signs. These hens were treated again on day 21 with diazinon (11.3 mg/kg) and observed for a further 3 weeks. One hen exhibited a slight unsteadiness in walking on day 41. On day 43, the hens were sacrificed and brain, spinal cord, and peripheral nerve from control, positive control, and treated hens were prepared for histopathology. Histopathological examination revealed no lesions consistent with delayed neurotoxicity in the control or treated hens, although these lesions were seen in the positive control hens.

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

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to diazinon. Limited information from laboratory experimentation indicated that, although oral diazinon exposure did not produce any significant effects on reproduction in four generations of rats, testicular atrophy

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and arrested spermatogenesis were seen in dogs. In one study, no adverse effects on reproduction were reported for mature female Sprague-Dawley rats fed 0.05 mg/kg/day diazinon in the diet for 60 days prior to weaning for 4 generations. 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 5 generations (F₀-F₄) of offspring (Green 1970). In another study in 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 in doses ranging from 2.5 to 20 mg/kg/day for 8 months. Testicular atrophy with completely arrested spermatogenesis was observed only in the one male dog of the 10 mg/kg/day group that lost weight and evidenced other gross pathological changes. All 3 male dogs in the 20 mg/kg/day group suffered similar effects (testicular atrophy observed in 2 of 3, arrested spermatogenesis observed in 1 of 3) (Earl et al. 1971).

Administration of diazinon at 10, 20, or 100 mg/kg/day diazinon by oral gavage during gestation days 6-15 in CD-1 rats had no significant effect on litter sizes or numbers of viable fetuses (Infuma et al. 1985). Maternal toxicity was noted at 100 mg/kg/day with a significant reduction in feed consumption and body weight gain. In New Zealand rabbits dosed by gavage at 7, 25, or 100 mg/kg/day diazinon during gestation days 6-18, no differences with controls were seen in number of implantations, proportion of live, dead or resorbed fetuses, fetal weights, or fetal sex ratios (Harris 1981). Nine of 22 does treated at 100 mg/kg/day died during the course of the study so significant maternal toxicity at this dose was observed.

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 (groups of 15 of each sex) exposed to up to 168 mg/kg/day diazinon (males) or 212 mg/kg/day (females) for 13 weeks via feed (Singh 1988), or exposed up to 10 mg/kg/day (males), or 12 mg/kg/day (females) for 98 weeks (Kirchner et al. 1991), or in Beagle dogs (groups of 4 of each sex) exposed to-up to 10.9 mg/kg/day (males) or 11.6 mg/kg/day (females) (Barnes 1988).

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

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2.2.2.6 Developmental Effects

No studies were located regarding developmental effects of diazinon in humans after oral exposure. Laboratory animal studies with mice provide evidence that exposure to diazinon via mother's milk does not result in neonatal toxicity. Results of toxicity evaluation in rats, mice, hamsters, and rabbits also indicate that oral exposure to diazinon does not have 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.

Pregnant Wistar rats given single doses of 52.6 or 63.5 mg/kg on gestation day 10 resulted in no deaths, and multiple doses of 6.6-17.3 mg/kg/day given on gestation day 8-12 or 12-15 resulted in only one maternal death. Little effect was observed on average fetal weight. Implantation per dam was not affected, but higher doses (70.6, 89.9, 95.2 mg/kg) increased fetal resorptions; this effect was seen only at the lowest dose tested (68.3 mg/kg) in rats treated only on gestation day 9. Both visceral (hydronephrosis, hydronephrosis) and skeletal (rudimentary/short/wavy ribs, irregular bone contours, hypocalcification) abnormalities were observed only at the lowest dose tested (68.3 mg/kg) (Dobbins 1967).

In a teratology study, a mouse dihybrid F_2 strain, obtained by crossing F_1 (female C57BL/6 x male A/JAX) with F_1 hybrid HC (female C3WHe x male Balb/c) was used as a more vigorous strain that was well-buffered against spontaneous congenital deformities. Dams were exposed to doses of 0, 0.18, or 9 mg/kg/day diazinon in peanut butter throughout gestation. The study found no maternal toxicity at any of the doses tested. However, the study reported significantly elevated ($p < 0.05$) mortality (12%, 18 of 150) in the high dose group at weaning (postpartum day ZS), 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 mortality from after weaning. Exposure to diazinon via mother's milk did not have any adverse effect (Bamett et al. 1980). A previous study using the same protocol and dose regimen exposed dams throughout gestation to doses of 0, 0.18, or 9 mg/kg/day diazinon in peanut butter (Spyker and Avery 1977). Dams exposed to either diazinon dose experienced reduced weight gain (86% that of controls, $p < 0.05$) during

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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 II 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 mice 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, 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 8 dams on gestation day 6, 7, and 8; 0.25 mg/kg/day to 5 dams on gestation day 7 or 8). All dams evidenced cholinergic signs of diarrhea, salivation, ataxia, but no deaths. 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 in maternally lethal doses. When pregnant New Zealand white rabbits were orally exposed by gel capsules to 7 or 30 mg/kg/day diazinon on gestation day 15, 6 of 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 (average number of fetuses per litter, fetal mortality, average fetal weight) effects were observed even at maternally toxic doses (Robens 1969). In another study where New Zealand rabbit does were exposed by gavage to 7, 25, or 100 mg/kg/day diazinon during gestation days 6-18 and sacrificed on

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gestation day 25, no significant treatment-related fetal malformations or skeletal malformations were observed in the offspring (Harris 1981). Nine of the 22 does in the 100 mg/kg/day group died during the study, indicating that significant maternal toxicity took place 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 (Infuma et al. 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 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

Chronic occupational exposure to multiple insecticides, including diazinon, has been associated with increased incidence of chromosomal aberrations and increased sister chromatid exchanges in peripheral blood lymphocytes compared with non-exposed populations (de Ferrari et al. 1991; Kiraly et al. 1979; See et al. 1990). Some of these exposures are presumed to be oral. 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.

No studies were located regarding genotoxic effects in animals after oral exposure to diazinon. Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 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. However, it is not possible to attribute the increased cancer incidence exclusively to diazinon exposure. Some of the exposure is presumed to have occurred by the oral route.

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

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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 non-farmers. 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 (0.3%) of the cases and 5 (0.3%) of the controls (Morris et al. 1986).

In laboratory animal studies, a cancer bioassay was conducted with groups of 100 (50 male, 50 female) Fischer 344 rats in which the rats were exposed *ad libitum* to an estimated 0, 20, or 40 mg/kg/day dose of diazinon in their feed for 103 weeks. Rats (25 of each sex) were used as 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 non-neoplastic lesions were observed with approximately equal frequency in the control and dosed groups in both sexes. An increase in the common lesion of endometrial stromal polyps was observed in female rats (control = 2 of 23, low dose = 8 of 43, high dose = 11 of 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 of 50), but not in the high dose group (12 of 50), relative to controls (5 of 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 100 (50 of each sex) B6C3F₁ mice were exposed for 103 weeks to dietary concentrations of 0, 13, or 26 mg/kg/day. Fifty mice (25 of each sex) were used as controls. A number of neoplastic and non-neoplastic lesions, essentially considered non-treatment-related, were observed in both the control and treated mice. An elevation in hepatocellular adenomas and carcinomas was observed in low-dose mice (20 of 46), but not in the high-dose mice (13 of 48), relative to controls (5 of 21). The study concluded that diazinon was not carcinogenic under the conditions of this assay for either sex of B6C3F₁ mice (NCI 1979).

2.2.3 Dermal Exposure

2.2.3.1 Death

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

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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 and solvents used. 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 mg/kg and 455 mg/kg for males and females, respectively. The dermal LD₅₀ of emulsifiable solution of diazinon was determined in male Wistar rats (Noakes and Sanderson 1969). When applied doses were occluded by a plaster cover backed with aluminum foil, LD₅₀ values were 1,100 mg/kg and 500 mg/kg after 4 and 24 hours, respectively. In another study, either emulsified solution or wettable powder formulations of diazinon were applied on the shaved skin of male Wistar rats. Applications were covered with a “plastic girdle” which was removed after 20 hours when the animals were thoroughly decontaminated by washing. No deaths or clinical signs were observed during the 7-day observation period after a maximum dose of 1000 mg/kg (Edson and Noakes 1960). Among New Zealand rabbits dermally exposed for 24 hours at 2,020 mg/kg to the diazinon MG-8 formulation (purity not reported but probably about 87%), 2 of 5 females died 2 days after exposure ceased (Kuhn 1989b). None of five males died.

A total of 25 male and 91 female sheep was dipped (5 minutes for adults and 3 minutes for lambs) in a 0.02% emulsion of diazinon (Smith 1970). One of 23 ewes and 1 of 3 ewe lambs died after exhibiting salivation, fasciculation, dyspnea, lethargy, ataxia, and miosis. Whole blood cholinesterase activity was reduced.

The LD₅₀ values and doses associated with death in each species and duration category are shown in Table 2-3.

2.2.3.2 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.

Table 2-3. Levels of Significant Exposure to Diazinon - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
ACUTE EXPOSURE						
Death						
Rat (Sherman)	once				900 M (LD ₅₀) mg/kg 455 F (LD ₅₀) mg/kg	Gaines 1960
Rat (Wistar)	4 or 24 hr				1100 M (estimated LD ₅₀ , 4-hour) mg/kg 500 M (LD ₅₀ , 24-hour) mg/kg	Noakes and Sanderson 1969
Systemic						
Human	72 hr	Dermal	1%			Lisi et al. 1987
Gn Pig (Hartley)	24 hr	Dermal	5% F	10% F (erythema)		Matsushita et al. 1985
Rabbit (New Zealand)	4 hr	Dermal		0.5 mL (erythema, slight edema)		Kuhn 1989a
Immunological/Lymphoreticular						
Human	once		1%			Lisi et al. 1987
INTERMEDIATE EXPOSURE						
Systemic						
Rat (dark agouti)	12 wk 7 d/wk 1 x/d	Hepatic		114 F (elevated fecal porphyrin) mg/kg		Bleakeley et al. 1979

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

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
Immunological/Lymphoreticular						
Gn Pig (Hartley)	24 hr			0.05% F (moderate delayed contact sensitivity)		Matsushita et al. 1985

d = day(s); F = female; Gn pig = Guinea pig; hr = hour(s); LD₅₀ = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level; NS = not specified; wk = week(s); x = times

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Respiratory Effects. A 56-year-old female gardener, dermally exposed to spilled diazinon of unknown purity, developed respiratory distress as a component of the spectrum of the symptoms of cholinergic effects resulting from acetylcholinesterase 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 of the diazinon MG-8 formulation (Kuhn 1989b). The purity of this formulation was not reported but was probably about 87% based on similar reports for the MG-8 formulation reported by the manufacturer, Ciba-Geigy.

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. In a case report, 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 of the diazinon MG-8 formulation (Kuhn 1989b). The purity of this formulation was not reported but was probably about 87% based on similar reports for the MG-8 formulation reported by the manufacturer, Ciba-Geigy.

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 (as 85% technical grade solution). Significant elevations in total fecal porphyrin excretion were observed at the 114 mg/mg/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

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were observed. Electrophoretic analysis revealed the presence of isocoporphyrin in the feces. Except for the unexplained lack of urinary porphyrin, these findings were noted to be biochemically characteristic of human porphyria cutanea tarda, and indicative of disturbed hepatic porphyrin metabolism. However, oral administration of 46 mg/kg/day to another group of rats was without this effect (Bleakley et al. 1979).

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

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

Skin erythema was noted in guinea pigs dermally exposed to 10 and 20% diazinon, but not at lower concentrations of 0.5-5.0% (Matsushita et al. 1985). The purity of the diazinon used was not reported in this study. 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 the diazinon MG-8 formulation (Kuhn 1989a). The purity of this formulation was not reported, but was probably about 87% based on similar reports for the MG-8 formulation reported by the manufacturer, Ciba-Geigy.

Body Weight Effects. Body weight was unaffected in New Zealand rabbits dermally exposed to up to 2,020 mg/kg for 24 hours to the diazinon MG-8 formulation (purity not reported but probably about 87%) and observed for a further 14 days (Kuhn 1989b).

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2.2.3.3 Immunological and Lymphoreticular Effects

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

Diazinon has also been tested for delayed contact hypersensitivity following skin application to guinea pigs. Induction concentrations of diazinon were reported as 5% (intradermal) and 25% (topical). At both 24 and 48 hours after challenge in the guinea pig maximization test, response to a 0.05% diazinon challenge was scored as grade III (moderate, 30% sensitization rate), and to 0.5% diazinon as grade V (extreme, 100% rate). When cross-sensitization was tested using a challenge of 0.2 or 2% benomyl, allergenicities were grade I (0%) and grade III (30%), respectively (Matsushita et al. 1985). Skin sensitization did not occur in Hartley guinea pigs treated 11 times over a 36-day period with 0.5 mL of the diazinon formulation MG-8 (purity not reported but probably about 87%) (Kuhn 1989~).

2.2.3.4 Neurological Effects

In a case report, 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 serum cholinesterase levels (Lee 1989).

Tremors were reported in female New Zealand rabbits but not males after 24 hours of dermal exposure to 2,020 mg/kg of the diazinon formulation MG-8 (purity not reported but probably about 87%) (Kuhn 1989a).

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

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2.2.3.5 Reproductive Effects

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

Within 36-48 hours after the dipping of 25 male and 91 female sheep, premature (by 3 months) ovulation and estrus were observed in 5 of 23 ewes (Smith 1970). Toxic effects were limited only to the Dorset Down breed, which suggests a partial species-specific response.

2.2.3.6 Developmental Effects

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

2.2.3.7 Genotoxic Effects

Chronic-duration occupational exposure to multiple insecticides, including diazinon, has been associated with increased incidence of chromosomal aberrations and increased sister chromatid exchanges in peripheral blood lymphocytes compared with non-exposed populations (de Ferrari et al. 1991; Kiraly et al. 1979; See et al. 1990). Some of these exposures are presumed to be through the skin. 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. No studies were located regarding genotoxic effects in animals after dermal exposure to diazinon. Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 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. However, it is not possible to attribute the increased cancer incidence exclusively to diazinon exposure. Some of the exposure is presumed to have occurred by dermal 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 non-farmers. 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 (0.3%) of the cases and 5 (0.3%) of the controls (Morris et al. 1986).

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

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

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

2.3.1.2 Oral Exposure

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 confirmed the rapid absorption of diazinon following oral administration of [¹⁴C]diazinon. 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 for 10 consecutive days of [¹⁴C]diazinon. 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). In goats given daily oral doses of 0.5 or 5.0 mg/kg/day diazinon for

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7 days or a single 150 mg/kg or 700 mg/kg dose, diazinon was detected from the first day of treatment (Mount 1984). Other studies demonstrated rapid absorption of orally administered diazinon in sheep (Janes et al. 1973; Machin et al. 1971, 1974) and in cows (Abdelsalam and Ford 1986).

2.3.1.3 Dermal Exposure

Volunteers were exposed for 24 hours to [¹⁴C]diazinon applied to either the forearm or abdomen in acetone or lanolin wool grease (Wester et al. 1993). Absorption was determined to be 34% of the applied dose with no difference related to vehicle or the area applied.

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

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

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

2.3.2.2 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 were found in the blood, followed by stomach contents and the bile. Lowest concentrations were found in the kidney, followed by adipose tissue, and then bile. Animal studies confirmed the human case study in that diazinon is widely distributed in all analyzed tissues in rats (Mticke et al. 1970), in sheep (Janes et al. 1973; Machin et al. 1971, 1974), and in cows (Abdelsalam and Ford 1986).

2.3.2.3 Dermal Exposure

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

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2.3.2.4 Other Exposure

Two female Beagle dogs received a single intravenous dose of 0.2 mg/kg [¹⁴C]diazinon in ethanol. Radioactivity in the blood decreased in a biphasic manner. The half-life of the terminal or elimination phase was estimated to be 1.5 hours (Iverson et al. 1975). Diazinon was found (5 mg/kg) in omental fat of a man found unconscious and who died 11 days later (Kirkbride 1987). Pesticide exposure was suspected in his death but no confirmatory test of acetylcholinesterase activity was performed, nor were clinical signs of diazinon toxicity reported. This man worked at a horticultural supply store and was an active gardener, however no route of exposure to the diazinon could be confirmed.

2.3.3 Metabolism

2.3.3.1 Inhalation Exposure

Diethylthiophosphate (DETP), a potential diazinon metabolite, was found in urinary samples from pest control operators exposed to diazinon by inhalation (Weisskopf et al. 1988).

2.3.3.2 Oral Exposure

Diazinon was the only chemical detected in the body fluids and tissues from a woman who died after ingesting a lethal dose estimated at 293 mg/kg of a diazinon formulation ("FERTI-LOME" bagworm spray) containing 10% diazinon (Poklis et al. 1980). A report on 5 individuals (3 males, 2 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 diazinon in serum and several metabolites (monoethyl phosphate, diethyl phosphate, diethyl phosphorothioate) in the urine (Klemmer et al. 1978). In rats given a single oral dose of unlabeled diazinon and ring-labeled [¹⁴C]diazinon, complete degradation of the pyrimidine ring to ¹⁴C₂ did not take place. Hydrolysis of the ester bond yielding 2-isopropyl-4-methyl-6-hydroxypyrimidine and diethyl phosphate (diazoxon) or diethyl phosphothiorate (diazinon) was determined to be the main degradative pathway of labeled diazinon (Machin et al. 1975; Mücke et al. 1970).

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2.3.3.3 Dermal Exposure

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

2.3.3.4 Other Exposure

Diethyl phosphorothioic acid and diethyl phosphoric acid have been identified as metabolites of [¹⁴C]diazinon following a single intravenous injection in female Beagle dogs (Iverson et al. 1975). In vitro metabolism of ethoxy-1-[¹⁴C]diazinon was carried out using rat liver microsomes (Yang et al. 1971). Diazinon was metabolized in a complex reaction via cytochrome P-450 to diazoxon and 2-isopropyl-4-methyl-6-hydroxypyrimidine. Diazoxon hydrolysis was catalyzed by microsomal enzymes without requiring NADPH to yield diethyl phosphoric acid. Diazoxon did not undergo desethylation reaction. Similar results were obtained using liver microsomes from sheep, cow, pig, rat, turkey, chicken, and duck (Machin et al. 1975).

The proposed metabolic pathway of diazinon (Aizawa 1989; Yang et al. 1971) is shown in Figure 2-3.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

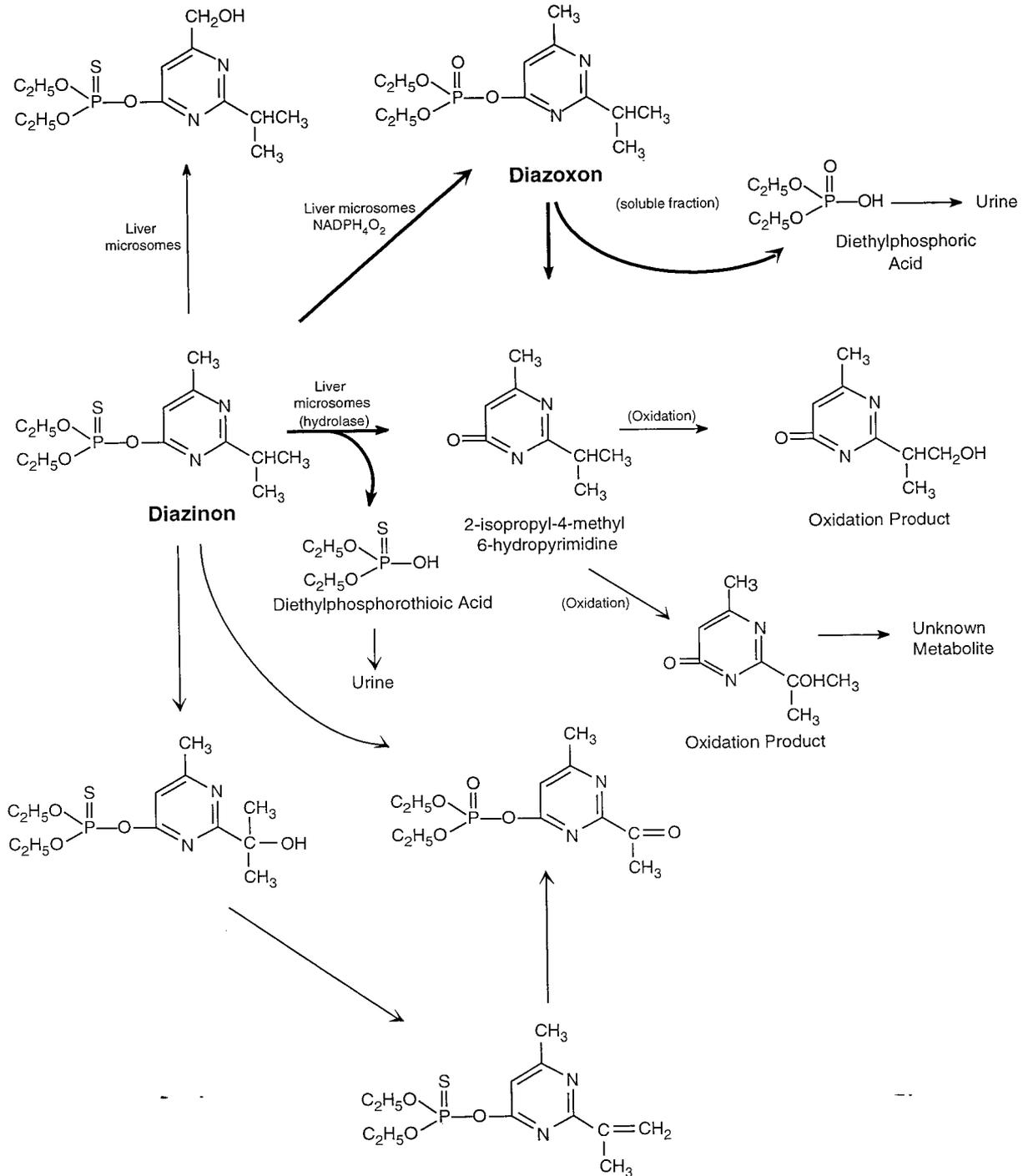
No studies were located regarding excretion of diazinon after inhalation exposure in animals or humans.

2.3.4.2 Oral Exposure

Following a single oral dose of 4.0 mg/kg 2-pyrimidinyl ring-labeled and 4-pyrimidinyl ring-labeled [¹⁴C] 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-[¹⁴C]diazinon dose was recovered as ¹⁴CO₂ in expired air. No ¹⁴CO₂ was expired from rats given an oral dose of 2-[¹⁴C] or 4-[¹⁴C]pyrimidine diazinon

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Figure 2-3. Proposed Mammalian Metabolic Pathway for Diazinon



Source: Adapted from Aizawa 1989; Yang et al. 1971

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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 (Mickel 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 2 metabolites which 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, diethyl phosphorothioate was detected in the urine but not in the milk (Mount 1984).

2.3.4.3 Dermal Exposure

Human 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 $\mu\text{g}/\text{dose}$ for each application method to test the percutaneous absorption of diazinon. Daily complete void urine samples were collected and analyzed for levels of radioactivity for 7 days after dosing. Percutaneous absorption, calculated from the amount of radioactivity present in the urine, was reported as 2.9-3.85% of the administered dose (Wester et al. 1993).

2.3.4.4 Other Exposure

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

2.4 MECHANISMS OF ACTION

Diazinon toxicity results predominantly from the inhibition of acetylcholinesterase in the central and peripheral nervous system. The enzyme is responsible for terminating the action of the neurotransmitter, acetylcholine, in the synapse of the pre- and post-synaptic nerve endings or in the neuromuscular junction. However, the action of acetylcholine does not persist long as it is hydrolyzed by the enzyme, acetylcholinesterase, and rapidly removed. As an anticholinesterase organophosphate, diazinon inhibits acetylcholinesterase by reacting with the active site to form a stable phosphorylated

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complex which is incapable of destroying acetylcholine at the synaptic gutter between the pre- and post-synaptic 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 post-ganglionic 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. Muscarinic effects 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 acetylcholinesterase, 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; Edson and Noakes 1960; Enan et al. 1982; Harris et al. 1969; Rajendra et al. 1986; Takahashi et al. 1991).

The primary cause of death in acute diazinon poisoning is a depression of the neurons in the brainstem (medulla), collectively known as the respiratory center, resulting in loss of respiratory drive or, in the case of managed treatment, cardiac failure due to electrical impulse or beat conduction abnormalities in cardiac muscles (fatal arrhythmias). Other effects, such as bronchoconstriction, excessive bronchial secretions, and paralysis of the respiratory muscles (intercostal muscles and diaphragm) may also contribute to respiratory insufficiency and death. Thus, death results from loss of respiratory drive and paralysis of the respiratory muscles, or cardiac failure, or both, with attendant asphyxia or cardiac arrest (Klaassen et al. 1986; Shankar 1967, 1978; Williams and Burson 1985).

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2.5 RELEVANCE TO PUBLIC HEALTH

Diazinon is an insecticide with broad-based use in both agriculture and in control of pests in residential dwellings, gardens, and on household pets. Like most organophosphorus insecticides, diazinon and its active metabolite diazoxon are rapidly hydrolyzed to non-toxic products. By far the greatest potential for significant exposure to this compound is found in occupational settings (i.e., manufacture and application of diazinon). The most common exposure scenario for the general population comes from home use of the product to control garden pests, application to animals in the form of shampoos, and residual contamination following indoor application for the control of insects. In all of the studies reviewed which reported an association between diazinon exposure and adverse health effects in humans, the levels of known or potential exposure to diazinon suggested direct contact and use of the compound or exposure to a treated environment. No association has been reported between diazinon toxicity and low level environmental contamination.

As an anticholinesterase organophosphate, the principal toxic effect of diazinon in humans and laboratory animals is inhibition of acetylcholinesterase (Coye et al. 1987; Davies and Holub 1980a, 1980b; Edson and Noakes 1960; Enan et al. 1982; Harris et al. 1969; Rajendra et al. 1986; Takahashi et al. 1991; Wecker et al. 1985). Inhibition of acetylcholinesterase 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. Severe acetylcholinesterase inhibition often leads to cholinergic symptoms in humans and laboratory animals which include excessive glandular secretions (salivation, lacrimation, rhinitis), miosis, bronchoconstriction, vasodilation, hypotension, diarrhea, nausea, vomiting, urinary incontinence, and bradycardia. Tachycardia, mydriasis, fasciculations, cramping, twitching, muscle weakness, and muscle paralysis are associated with nicotinic receptor stimulation. Central nervous system toxicity includes respiratory depression, anxiety, insomnia, headache, apathy, drowsiness, dizziness, loss of concentration, confusion, tremors, convulsions, and coma. In non-fatal exposures, the effects are transient and recovery is rapid and complete following cessation of exposure (Bichile et al. 1983; Hata et al. 1986; Klemmer et al. 1978; Reichert et al. 1977; Wadia et al. 1974; Wedin et al. 1984). In sufficiently high doses, death may result in some cases (Kabrawala et al. 1965; Limaye 1966; Poklis et al. 1980). These effects usually occur within a few minutes to 24 hours after dosing, depending on the extent of exposure.

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Minimum Risk Levels (MRLs) for Diazinon.

Inhalation MRLs.

- An MRL of 0.009 mg/m³ has been derived for intermediate-duration inhalation exposure (15-364 days) to diazinon.

This MRL is based on a NOAEL of 0.46 mg diazinon/m³ for brain acetylcholinesterase inhibition (the target of diazinon toxicity) observed in a 21-day study in hybrid rats (Hartman 1990). Groups of rats (10 of each sex) were exposed to control air or air containing 4 different concentrations of aerosolized diazinon (0.05, 0.46, 1.57, or 11.6 mg/m³) for 6 hours a day, 5 days a week for 3 weeks. Compared to control, no clinical signs of organophosphate neurotoxicity were observed or any effect on survival or body weight. Histopathology of the nasal tract and lungs was normal in all groups, as was the spleen, heart, liver, kidney, and adrenal gland (examined only in the 11.6 mg/m³ groups). A dose-response relationship existed for both erythrocyte and brain acetylcholinesterase in the female rats, and a NOAEL of 0.46 mg diazinon/m³ was identified. This level was converted to a Human Equivalent Concentration to adjust for the different penetration of aerosols in the human and rat respiratory tract (see Appendix A) and also adjusted for intermittent versus constant exposure. An uncertainty factor of 30 (3 for animal-to-human extrapolation and 10 for human variability) was applied resulting in a MRL of 0.009 mg/m³.

Acute- and chronic-duration inhalation exposure MRLs for diazinon were not derived because of a lack of suitable studies in the literature. Since diazinon is not volatile, inhalation exposure near toxic waste sites is probably less likely than oral or dermal exposure. However, the potential risk of adverse health effects from inhalation exposure to diazinon cannot be assessed without information on the levels actually present in the air around the site. The MRL level of 0.009 mg diazinon/m³ should be protective for individuals living near waste sites. NIOSH has recommended a Permissible Exposure Level (PEL) of 0.1 mg diazinon/m³ to protect the health of individuals who regularly use diazinon in their work; the MRL level of 0.009 mg/m³ is approximately 100-fold lower.

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Oral MRLs.

- An MRL of 0.0002 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to diazinon.

This MRL is based on a NOAEL of 0.02 mg/kg/day for brain acetylcholinesterase inhibition in Beagle dogs receiving diazinon in their food daily for 13 weeks (Barnes 1988). Groups of 4 dogs of each sex consumed 0, 0.0034, 0.02, 5.9, or 10.9 mg diazinon/kg/day (males) or 0, 0.0037, 0.021, 5.6, or 11.6 mg diazinon/kg/day (females) for 13 weeks. No deaths occurred during the study. Emesis and diarrhea were reported in all groups, but the effects were not dose-related. No histopathological evidence of treatment-related effects were seen in brain, spinal cord, peripheral nerve, or optic nerve. A dose-response for brain acetylcholinesterase inhibition was demonstrated in the two highest dose groups in both sexes and a NOAEL of 0.02 mg/kg/day was observed. The MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (10 for animal-to-human extrapolation and 10 for human variability).

An MRL for acute-duration oral exposure was not derived because information on the purity of the diazinon used was unavailable in most of the studies for this duration of exposure. A NOAEL of 0.05 mg/kg/day for brain acetylcholinesterase inhibition was identified in a chronic-duration study on diazinon in rats (Kirchner 1991). However, the chronic-duration MRL derived from this study would be 0.0005 mg/kg/day. Since the intermediate-duration MRL (0.0002 mg/kg/day) would be more protective, it was the only one derived. This MRL should be protective for individuals living near hazardous waste sites. The most likely means by which oral exposure to diazinon would occur at a waste site would be via contamination of drinking water or the unintentional ingestion of contaminated groundwater or soil. Measurement of diazinon levels in these media would be necessary to assess whether any harmful effects might occur. It is known from studies in rats (Kirchner 1991; Singh 1988) and dogs (Barnes 1988) that oral exposure at approximately 100-fold higher than the MRL level is necessary before inhibition of the most sensitive biomarker for diazinon exposure (serum acetylcholinesterase) can be demonstrated. Serum cholinesterase inhibition alone has never been associated with toxicity.

Death. In most cases of diazinon-related deaths in humans, the amount of the insecticide ingested is not known. Thus, an estimate of the minimally lethal dose is not possible. One study reported that

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the ingestion of approximately 293 mg/kg of a 10% diazinon formulation was fatal in a 54-year-old woman (Wecker et al. 1985). In rats, the oral LD₅₀ for technical diazinon for both sexes ranges from 76 to 300 mg/kg (Enan et al. 1982; Gaines 1960, 1969; Takahashi et al. 1991), which is in the dose range estimated to be fatal in other human reports (Wecker et al. 1985). Long-term exposure to 10 mg/kg/day diazinon in dogs caused 30% mortality after 8 months (Earl et al. 1971).

No reports of human deaths resulting from dermal exposure to diazinon were located, but evidence from non-lethal human data and animal lethality studies indicates that human lethality by these routes of exposure is unlikely (Edson and Noakes 1960; Gaines 1960; Lee 1989; Noakes and Sanderson 1969).

Systemic Effects.

Respiratory Effects. In humans and laboratory animals, acute exposure to sufficiently high doses (as found in accidental ingestion or suicide attempts) led to respiratory distress as a component of the spectrum of the symptoms of cholinergic effects resulting from acetylcholinesterase inhibition. In a human study, acute oral doses of diazinon induced pulmonary distress in the poisoned victims by causing bronchoconstriction, increased bronchial secretions, pulmonary edema, active hyperemia, hypostatic congestion, and pneumonia (Poklis et al. 1980; Shankar 1967). A 56-year-old female gardener, dermally exposed to spilled diazinon of unknown purity, developed pulmonary edema with bilateral lung crepitations and tachypnea (Lee 1989). In rats, single oral doses of 50-700 mg/kg diazinon produced pulmonary inflammation, vascular congestion, venous stasis, and occasional extensive pneumonitis (Boyd and Carsky 1969). The most common cause of death in that study was respiratory failure, which is in keeping with the postulated mechanism of diazinon-related deaths.

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). In dogs, diazinon was associated with an absence of pericardial fat (Earl et al. 1971). Additionally, diazinon-related elevations in serum LDH were also found. This is a nonspecific response that may be suggestive of either cardiac or skeletal muscle damage, or some other unknown biological activity (Earl et al. 1971).

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Gastrointestinal Effects. Acute pancreatitis (as well as other gastrointestinal disturbances) appears to be a component of high acute diazinon intoxication in humans, manifesting as a secondary effect of the spectrum of cholinergic reactions by some unknown mechanism. Oral exposure to diazinon has been shown to cause gastrointestinal irritation, ulceration, and congested stomach mucosa with submucosal petechial hemorrhage in humans (Poklis et al. 1980). 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). Dermal exposure to diazinon in humans also produced gastric irritation and 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). In animal studies, oral exposure to high acute diazinon doses has resulted in gastrointestinal tract histopathology as well (Boyd and Carsky 1969).

Hematological Effects. Diazinon exposure is not likely to produce adverse effects on the blood and bone marrow in humans. Hematological analysis performed on samples from 5 individuals (3 males, 2 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, hemoglobin, and hematocrit were all within normal ranges (Klemmer et al. 1978). Although two female gardeners, dermally exposed to spilled diazinon, developed hypokalemia and leucocytosis, these symptoms were not observed in any other human study with diazinon. Furthermore, the purity of the diazinon in this exposure is unknown; therefore, these effects may be due to impurities or other chemical compounds in the formulation of the diazinon sample (Lee 1989). In animal studies, male rats acutely exposed to oral doses of up to 4.4 mg/kg diazinon exhibited reduced platelet counts and fibrinogen activity; the activity of other clotting components (prothrombin, partial thromboplastin, factor II, factor V, and factor X) was increased (Lox 1983). Since fibrinogen and factors II, V, and X are synthesized in the liver, however, the changes in clotting factor activity may be the result of diazinon-induced hepatic toxicity. Similar results were noted in a 14-day study using a single dose of 52 mg/kg in female rats (Lox 1987) and a 6-month study using a single dose of 0.18 mg/kg in female rats (Lox and Davis 1983). However, these results may not be reliable because the factor-deficient substrates used to measure the rat plasma activities were of human origin and, therefore, the observations might reflect some degree of cross-species differences. In addition to affecting clotting, oral exposure to diazinon in dogs has been shown to cause anemia, perhaps, by directly affecting the

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bone marrow since elevations in the myeloid/erythroid ratio were found (Earl et al. 1971). In pigs, intermediate-duration exposure to diazinon also caused anemia, reticulocytopenia, and an elevated myeloid/erythroid ratio (Earl et al. 1971). But there is no evidence that similar effects occur in humans.

Musculoskeletal Effects. Diazinon exposure is not likely to produce irreversible adverse effects on the muscle and skeleton in humans. No musculoskeletal effects were reported in humans from exposure to diazinon by the oral route. One study reported mild pathologic changes in the intercostal muscles of a man who died after inhaling a large dose of diazinon. Acetylcholinesterase activity in that man was found to be 50% lower than normal, which is consistent with organophosphate (diazinon) exposure (Wecker et al. 1985). In animals, acute oral exposure to diazinon in dogs elevated serum LDH. This is a nonspecific response that may be suggestive of either cardiac or skeletal muscle damage or some other unknown biological activity (Earl et al. 1971).

Hepatic Effects. No hepatic effects were reported in humans from exposure to low doses of diazinon by any route. Hepatic effects reported in human studies were associated with acute high levels of diazinon such as are found in suicide attempts (Limaye 1966). The acute- and intermediate-duration oral exposure to diazinon in animals reduced the activity of a variety of hepatic enzymes (Anthony et al. 1986; Mihara et al. 1981). Liver pathology has also been observed in animals following chronic oral exposure to diazinon. The pathological changes reported in one study included fatty infiltrations, parenchymal atrophy, hepatocyte dissociation, mild cirrhosis, and focal necrosis (Earl et al. 1971). The intermediate dermal exposure to diazinon increased fecal porphyrin excretion, indicating that diazinon may interfere with hepatic metabolism of porphyrins (Bleakely et al. 1979). However, it is not certain that similar effects would occur in humans following diazinon exposure.

Renal Effects. The evidence from humans and laboratory animals exposed to diazinon indicates that adverse renal effects may occur in humans after exposure to high acute doses of diazinon. Oral diazinon exposure in humans is associated with renal structural damage and altered kidney function (Poklis et al. 1980; Wedin et al. 1984); however, the effects may have been due to impurities or solvents present in the diazinon formulations. The deliberate ingestion of approximately 293 mg/kg of a diazinon formulation ("FERTI-LOME" bagworm spray; 10% diazinon) caused renal congestion, renal cortical submucosal petechiae, and ecchymoses (Poklis et al. 1980). In animals, single oral doses of diazinon ranging from 50 to 700 mg/kg produced dose-dependent renal toxicity (Boyd and Carsky

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1969). The effects included biochemical alterations (aciduria and alkaluria, hematuria, glycosuria, proteinuria, and hematuria) and renal structural damage (tubular swelling and capillary loop congestion). The toxicity was increased by protein deprivation prior to treatment (Boyd and Carsky 1969).

Endocrine Effects. Acute pancreatitis appears to be a component of severe acute diazinon intoxication in humans, manifesting as a secondary effect of the spectrum of cholinergic reactions by some unknown mechanism. Acute pancreatitis, as determined by blood chemistry analysis, was found in two children poisoned with an unknown quantity or formulation of diazinon (Weizman and Sofer 1992). A 16-year-old human female also exhibited pancreatitis following ingestion of 1.5 mg/kg of a diazinon formulation (Tik-20) (Dagli et al. 1981). 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 (Lee 1989).

Dermal Effects. Dermal exposure to diazinon resulted in contact dermatitis in farm workers (Matsushita et al. 1985). But in another human dermal exposure study, diazinon failed to elicit an irritation response (Lisi et al. 1987). In laboratory animal studies, diazinon was also not irritating to guinea pigs in a 24-hour occluded skin patch test (Matsushita et al. 1985).

Body Weight Effects. Body weight loss after exposure to diazinon is not likely to be a health effect of concern in humans. Although significant loss of body weight was observed in dogs given oral diazinon doses of ≥ 10 mg/kg, no clear dose-response for this effect was observed in the study. The observed body weight reductions were probably a result of reduced food intake, emesis, diarrhea, generalized emaciation, and anorexia reported in the study (Earl et al. 1971). No body weight reductions were reported in the available human studies.

Immunological and Lymphoreticular Effects. The potential for diazinon exposure to induce adverse immunological/lymphoreticular effects in humans is not certain. Acute oral diazinon exposure in rats has been shown to reduce spleen weight by 35%, cause splenic red pulp contraction, decrease thymus weight, and induce thymic atrophy (Boyd and Carsky 1969). The intermediate oral administration of diazinon to dogs caused splenic shrinking (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

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diarrhea, emesis, and anorexia, as reported in the study. It is not certain that similar effects would occur in humans following diazinon exposure.

Human subjects showed allergic interaction between the fungicide benomyl and diazinon following dermal exposure to these insecticides (Matsushita and Aoyama 1981). In animal dermal exposure studies, guinea pigs displayed an allergic interaction between the fungicide benomyl and diazinon (Matsushita and Aoyama 1981). Similarly, diazinon caused delayed contact hypersensitivity 24 and 48 hours after challenge in the guinea pig maximization test (Matsushita et al. 1985). When cross-sensitization was tested using a challenge of 0.2 or 2% benomyl insecticide, allergenicities were grade I (0%) and grade III (30%), respectively (Matsushita et al. 1985).

Neurological Effects. As an anticholinesterase organophosphate, diazinon inhibits blood and tissue acetylcholinesterase in mammals (Dagli et al. 1981; Davies and Holub 1980a, 1980b; Edson and Noakes 1960; Enan et al. 1982; Harris et al. 1969; Rajendra et al. 1986; Takahashi et al. 1991). In high acute doses, diazinon causes severe acetylcholinesterase inhibition that often leads to cholinergic signs and symptoms, manifest as reversible neuromuscular dysfunction when treated or when exposure is terminated. These manifestations include muscarinic effects (bronchoconstriction, increased bronchosecretion, nausea and vomiting, diarrhea, bradycardia, hypotension, miosis, urinary incontinence), nicotinic effects (tachycardia, hypertension, muscular twitching and weakness, fasciculation, cramping), and central nervous system effects (anxiety, apathy, depression, giddiness, drowsiness, insomnia, nightmares, headaches, confusion, ataxia, depressed reflex, seizure, respiratory depression, coma). In sufficiently high exposures (such as are found in suicide attempts or accidental ingestions) death from respiratory failure may result without timely treatment intervention (Bichile et al. 1983; Dagli et al. 1981; Hata et al. 1986; Kabrawala et al. 1965; Klemmer et al. 1978; Reichert et al. 1977; Schenker et al. 1992; Shankar 1967, 1978; Wadia et al. 1974; Wedin et al. 1984). Similarly, inhalation exposure to high acute doses of diazinon may result in cholinergic signs and a variety of symptoms that stem predominately from acetylcholinesterase inhibition. In acute inhalation poisoning reports where both inhalation and dermal exposure may have occurred, victims exhibited neurological symptoms or cholinergic signs and symptoms that often resulted in death from respiratory or cardiac failure (Adlakha et al. 1988; Rayner et al. 1972; Richter et al. 1992; Soliman et al. 1982). The cholinergic manifestations of high acute exposure to diazinon have also been reported in animals and include anorexia, ataxia, epistaxis, tremors, listlessness, gasping, convulsions, tachypnea, dyspnea, prostration, fasciculations, twitches, exophthalmos, diarrhea, salivation, diuresis, lacrimation,

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prostration, Straub tail reflex, and hypothermia (Boyd and Carsky 1969; Earl et al. 1971; Takahashi et al. 1991; Williams et al. 1959). Protein deficiency may potentiate diazinon-induced toxicity (Takahashi et al. 1991), perhaps by limiting the hepatic synthesis of the enzymes necessary to metabolize diazinon.

Longer-term exposure to lower diazinon doses may lead to the development of subtle behavioral/cognitive ability deficits. A case study of 99 adult humans (67 males and 32 females) who had been potentially exposed to diazinon granules occupationally for 8 hours a day for 39 days during an insecticide application program reported manifestations of decreased post-shift symbol-digit speed and pattern memory accuracy (Maizlish et al. 1987). In one animal study, mice exposed to diazinon *in utero* exhibited signs of behavioral/functional deficits (as manifested by delayed contact placing and sexual maturity); they also exhibited endurance and coordination deficits: decreased performance on neuromuscular function tests (rod cling and inclined plane), slower running speed in a Lashley II maze, and reduced swimming endurance. These effects have been postulated to 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). Thus, prolonged low-level diazinon exposure in adult humans or *in utero* exposure may result in functional deficits in otherwise normal humans that can only be detected by systematic behavioral evaluation.

Reproductive Effects. Diazinon exposure is not likely to result in any significant reproductive effects in humans. No information was located on the reproductive effects of diazinon exposure in humans. Only three animal studies on the reproductive effects of diazinon exposure were located. The first study in rats found that oral diazinon exposure increased litter size (Green 1970), while a second rat study reported significant reduction ($p < 0.05$) in litter size at oral maternal diazinon doses of 0.18 and 9 mg/kg/day (Spyker and Avery 1977). A third study, a 4-generation study which used only 3 dogs per sex, reported a dose-response testicular atrophy and arrested spermatogenesis in males in the fourth generation of male dogs (Earl et al. 1971).

Developmental Effects. Diazinon exposure is not likely to result in significant developmental effects in humans. No information on the developmental effects of diazinon in humans from inhalation, oral, or dermal exposure was located. However, there is limited evidence that prenatal exposure to low levels of diazinon may result in functional deficits in otherwise normal animals that can only be detected by systematic behavioral evaluation (Spyker and Avery 1977). These slight

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neuromuscular deficits 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. Furthermore, several studies in laboratory animals report developmental anomalies in rats. One of these studies exposed rats during gestation to diazinon and concluded that prenatal diazinon exposure caused focal forebrain abnormalities typified by dense aggregations of atypical chromatin-containing cells in offspring. These offspring displayed slight neuromuscular deficit as manifested by decreased performance on rod clinging and inclined plane tests (Spyker and Avery 1977). Diazinon has also been reported to increase the number of fetal resorptions and increase the incidence of visceral (hydronephrosis, hydronephrosis) and skeletal (rudimentary, short, wavy rib; hypocalcification) variations at moderate doses (Dobbins 1967) and cause offspring growth retardation in rats in relatively low doses (Green 1970). However, the effects reported in these studies did not show dose-response. In addition, other studies conducted with hamsters and rabbits failed to result in any developmental effect in the offspring of these hamsters and rabbits. The maternal doses used in one of the studies that produced negative developmental effects in rabbits were sufficiently high to induce severe cholinergic reaction in the maternal rabbits (Robens 1969).

Genotoxic Effects. The genotoxic effects of diazinon in humans are not known because existing human data are inadequate and the results of *in vitro* laboratory testing data in mammalian cells and microorganisms are equivocal. Several reports that described potentially chronic occupational inhalation and dermal exposures to multiple insecticides, including diazinon, associated these exposures with increased incidence of chromosomal aberrations and increased sister chromatid exchanges in peripheral blood lymphocytes (De Ferrari et al. 1991; Kiraly et al. 1979; See et al. 1990). However, it is not possible to attribute these genotoxic effects exclusively to diazinon because the workers were concurrently or sequentially exposed to up to 80 different insecticides in unknown amounts for variable durations as indicated in these reports. In the laboratory, the mutagenicity of diazinon has been studied in a variety of test systems, with mixed results. *In vitro* test results show that diazinon was positive for gene mutations in the *Salmonella typhimurium* test 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). But in other tests, diazinon was negative for gene mutations in the *Salmonella typhimurium* test assay (Marshall et al. 1976) and in the recassay utilizing strains of *Bacillus subtilis* (Shirasu et al. 1976). Both of these studies were conducted without metabolic activation. Tests for sister chromatid exchange in Chinese hamster V79 cells, both

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with and without metabolic activation (Chen et al. 1982), and for chromosomal aberrations in human peripheral blood lymphocytes (Lopez et al. 1986), were also negative. Table 2-4 lists genotoxic effects of diazinon *in vitro*.

Cancer. There is no specific evidence from epidemiological studies that diazinon causes cancer in humans. Several studies have reported an increased incidence of cancers (brain tumors, Hodgkin's lymphoma, multiple myelomas) in humans who were concurrently or sequentially exposed to a number of insecticides, including diazinon (Cantor et al. 1992; Davis et al. 1993; Morris et al. 1986). However, it is not possible to attribute the increase in cancer incidence exclusively to diazinon exposure. Consequently, while the findings in these studies suggest an elevated risk for the cancers from high exposure to insecticides, in general, the data are far too limited to be used to evaluate the potential for diazinon to cause cancer in humans.

The evidence from animal studies suggest that diazinon exposure is not likely to cause cancers in humans. While not designed as a cancer bioassay, in a recent study where rats (groups of 20-30) were orally exposed to diazinon (Kirchner 1991) for 98 weeks, histopathology of some 30-40 different tissues showed no treatment-related increase in neoplasms. No carcinogenic effects in laboratory animals following inhalation or dermal exposure to diazinon were reported in any of the located studies. A short-term animal cancer bioassay conducted in mice by intraperitoneal administration of diazinon was associated with increased incidence of lung cancers in a strain of mice (A/St) that are naturally predisposed to this type of cancer (Maronpot et al. 1986). The positive conclusion in this study regarding the potential for diazinon to produce animal cancers and its relevance to human risk from cancers is questionable because of the predisposition of the strain of mice used in the study to develop the type of cancers observed in the study as well as the route of diazinon administration used in the study.

The National Cancer Institute (NCI) concluded that diazinon was not carcinogenic in either rats or mice following chronic bioassays in Fischer 344 rats and B6C3F₁ mice (NCI 1979).

2.6 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

Table 2-4. Genotoxicity of Diazinon *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Reverse mutation				
<i>B. subtilis</i> (rec assay)	Gene mutation	ND	–	Shirasu et al. 1976
<i>S. typhimurium</i>	Gene mutation	+	–	Wong et al. 1989
<i>S. typhimurium</i>	Gene mutation	ND	–	Marshall et al. 1976
Eukaryotic cells:				
Human peripheral blood lymphocytes	Chromosomal aberration	ND	–	Lopez et al. 1986
Mouse lymphoma cells	Gene mutation	ND	+	McGregor et al. 1988
Chinese hamster cells	Sister chromatid exchange	–	–	Chen et al. 1982
Chinese hamster cells	Chromosomal aberrations	+	–	Matsuoka et al. 1979

– = negative result; + = positive result; ND = Not done

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(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 (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to diazinon are discussed in Section 2.6.1.

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 2.6.2.

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 2.8, Populations That Are Unusually Susceptible.

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2.6.1 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; Mticke et al. 1970). 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 (Mucke 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 2-isopropyl-4-methyl-6-hydroxypyrimidine, diethyl phosphorothioic acid, and diethyl phosphoric acid have been reported following exposure of animals to diazinon (Aizawa 1989; Iverson et al. 1975; Machin et al. 1975; Mount 1984; Mticke et al. 1970; Yang et al. 1971) while diethyl phosphorothioic acid and diethyl phosphoric acid have been detected in the urine of exposed insecticide applicators (Maizlish et al. 1987). Analysis of blood samples for the presence of these metabolites represents a potential means of assessing exposure; however, only 2-isopropyl-4-methyl-6-hydroxypyrimidine is specific for diazinon. Analysis of urine samples for metabolic products provides a non-invasive 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 studies which report a quantitative association between metabolite levels and exposure to diazinon in humans. Therefore, these biomarkers are only indicative of exposure and are not useful for dosimetric analysis.

2.6.2 Biomarkers Used to Characterize Effects Caused by Diazinon

The major action resulting from human exposure to diazinon is the inhibition of cholinesterase activity (refer to Section 2.4 for discussion). Two pools of cholinesterases are present in human blood; acetylcholinesterase in erythrocytes and serum cholinesterase (sometimes referred to as pseudocholinesterase or butyrylcholinesterase) in plasma. Acetylcholinesterase, present in human erythrocytes, is identical to the enzyme present in neural tissue (the target of diazinon action) while serum cholinesterase has no known physiological function. Inhibition of both forms of cholinesterase have been associated with exposure to diazinon in humans and animals (Coye et al. 1987; Edson and Noakes 1960; Soliman et al. 1982). Inhibition of erythrocyte, serum, or whole blood cholinesterase 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.

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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 serum cholinesterase activity has been reported to be a more sensitive marker for diazinon exposure than erythrocyte acetylcholinesterase (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 post-exposure 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 cause 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.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.7 INTERACTIONS WITH OTHER CHEMICALS

The toxicity of diazinon may be affected by other substances. Some chemicals may increase the toxicity of diazinon in an additive manner. Anticholinesterase organophosphates and carbamates would be expected to act in an additive manner with diazinon with respect to its potential to induce cholinergic toxicity.

Other 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 enzymes of the liver. More than 200 drugs, insecticides, carcinogens, and other chemicals are known to induce the activity of liver microsomal drug-metabolizing enzymes. The characteristic

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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, heptachlorepoide, pyrethrins); steroid hormones (testosterone, progesterone, cortisone); and carcinogenic polycyclic aromatic hydrocarbons (3-methylcholanthrene, 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 the enzyme induction. Similarly, concurrent exposure to diazinon and MFO enzyme-inhibiting substances (e.g., carbon monoxide; ethylisocyanide; SKF 525A, halogenated alkanes, such as CCl_4 ; alkenes, such as vinyl chloride; and allelic and acetylenic derivatives) may increase the toxicity of diazinon by decreasing the rate of the hydrolytic dealkylation and hydrolysis of both parent diazinon and activated diazinon (diazoxon) (Williams and Burson 1985). The balance between activation and detoxification determines the biological significance of these chemical interactions with diazinon.

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 serum cholinesterase (Klaassen et al. 1986). Since serum cholinesterase is strongly inhibited by diazinon (Davies and Holub 1980b; Edson and Noakes 1960; Klemmer et al. 1978; Williams et al. 1959), it is possible that concurrent exposure to diazinon may result in the prolongation of the action of succinylcholine leading to prolonged muscular paralysis.

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2.8 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 include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects on clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

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). Therefore, low xenobiotic metabolizing activity could result in greater toxicity. The newborn of several animal species, including humans, have a reduced ability to metabolize xenobiotics and may be more sensitive to diazinon toxicity.

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, it is expected that dietary deficiency in protein would increase diazinon toxicity by diminishing its metabolism in the liver. Hereditary factors may also contribute to population sensitivity to diazinon. Atypical serum cholinesterase with low activity is present in a small percentage of the human population. This altered enzyme is the result of an hereditary factor with 0.04% occurrence in the population. Since serum cholinesterase is strongly inhibited by diazinon (Davies and Holub 1980b; Edson and Noakes 1960; Klemmer et al. 1978; Williams et al. 1959), it is expected that individuals who have atypical ChE (or low plasma cholinesterase 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 cholinesterase activity may also increase subpopulation sensitivity to diazinon exposure. This is because, after exposure, serum cholinesterase acts as a depot for diazinon due to its strong affinity for the substance (Davies and Holub 1980b; Edson and Noakes

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1960; Klemmer et al. 1978; Williams et al. 1959), thus decreasing the availability of the diazinon dose to the target (neuromuscular tissue) of diazinon toxicity in the population with normal plasma cholinesterase levels. In individuals with congenital low plasma cholinesterase activity, less diazinon is bound in the blood and more unbound diazinon is in circulation to reach the target of diazinon toxicity (neuromuscular tissue).

2.9 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.

2.9.1 Reducing Peak Absorption Following Exposure

Organophosphate insecticides like diazinon are rapidly absorbed after inhalation, ingestion, and dermal contact. In oral exposures, emesis is not indicated because of the danger of aspiration of stomach contents by an obtunded patient. Gastric lavage, with a solution of 5% sodium bicarbonate or 2% potassium permanganate, may be indicated within the first 60 minutes after ingestion to get rid of unabsorbed diazinon in the stomach (Shankar 1967, 1978). Activated charcoal can also be used but cathartics are not necessary due to the diarrhea induced by muscarinic activity. Decontamination is the first step in reducing dermal or eye contact absorption. This decontamination should begin immediately after the exposure is recognized. Contaminated clothing should be removed and skin (including hair and nails) should be washed copiously with soap and water. Health care workers and emergency responders should be protected from secondary contamination, and clothes and other contaminated material should be treated as contaminated waste. Eyes should be irrigated with copious amounts of room temperature water or saline, if available, for at least 15 minutes. Irritation, lacrimation, or especially pain, swelling, and photophobia persist after 15 minutes of irrigation, expert ophthalmologic care should be sought.

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If exposure is via inhalation, the exposed individual should be moved to fresh air and efforts should be directed toward the maintenance of an open airway, airway suctioning, endotracheal intubation. Artificial ventilation with supplemental oxygen may be helpful.

2.9.2 Reducing Body Burden

Diazinon is rapidly metabolized, with an estimated mammalian biological half-life of 12-15 hours (Iverson et al. 1975; Müccke 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 (Mucke et al. 1970; Poklis et al. 1980).

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

As an anticholinesterase organophosphate, the principal toxic effect of diazinon in humans and laboratory animals derive from inhibition of neural acetylcholinesterase (Coye et al. 1987; Davies and Holub 1980a, 1980b; Edson and Noakes 1960; 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, as manifested by 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 bronchorecretion; 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; Coyle 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).

Timely treatment of diazinon poisoning cases with atropine and 2-PAM significantly reduces the cholinergic effects (Harris et al. 1969; Klemmer et al. 1978; Shankar 1967, 1978).

Atropine is an anti-muscarinic agent which, in large doses, alleviates bronchoconstriction and reduces secretion in the oral cavity and the airway. Atropine also counters some of the central nervous system

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effects of organophosphates. Atropine should be given immediately by intravenous injection until evidence of “atropinization” or muscarinic blockade, such as flushing, dry mouth, dilated pupils, and tachycardia is seen. The most clinically important indication for continued atropine treatment is persistent wheezing (pulmonary rales) or bronchorrhea (Woo 1990). Pralidoxime (2-PAM) acts to regenerate inhibited acetylcholinesterase enzyme at all affected sites by displacing the diethylphosphoester bond diazinon forms at the active site. It should also be given immediately after diazinon poisoning is diagnosed and can be repeated to counter the nicotinic manifestations such as muscular weakness and fasciculations. Pralidoxime is most effective if started within the first 24 hours, preferably within 6-8 hours of exposure, prior to the irreversible phosphorylation of the enzyme (Schenker et al. 1992; Shankar 1967, 1978).

2.10 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.

2.10.1 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 2-4. 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 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

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Figure 2-4. Existing Information of 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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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* (ATSDR 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 2-4 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 2-4). 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 acetylcholinesterase inhibition.

2.10.2 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 information available on humans consists primarily of studies of cholinergic (neurological) reactions resulting from acetylcholinesterase inhibition. Effects noted include respiratory, cardiovascular, hematological, kidney, liver, gastrointestinal tract, endocrine, neurological, and immunologic/lymphoreticular system toxicity (Balani

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et al. 1968; Bichile et al. 1983; Dagli et al. 1981; De Palma 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; Edson and Noakes 1960; Enan et al. 1982; Gaines 1960, 1969; Harris et al. 1969; Krijnen and Boyd 1971; Noakes and Sanderson 1969) and cholinergic (neurological) reactions resulting from acetylcholinesterase inhibition. Effects noted include respiratory, gastrointestinal, hematological, liver, kidney, immunologic/lymphoreticular, and neurological toxicity (Boyd and Carsky 1969; Edson and Noakes 1960; 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 acetylcholinesterase inhibition, the diazinon exposure levels at which these effects begin to occur are usually not known. Similarly, the available animal studies provide adequate insight into the acetylcholinesterase inhibiting action of diazinon in acute oral exposures, but lack sufficient dose-response data for estimating protective levels for humans. In addition, most of the earlier reports on diazinon did not report information on the purity of the test substance. This is especially important for diazinon where degradation of improperly stabilized diazinon has been associated with human toxicity (Hayes 1982). Quantitative acute oral exposure information as well as information on the acute inhalation toxicity and toxicokinetics in both humans and laboratory animals would be helpful in developing acute oral and inhalation MRLs 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, musculoskeletal, renal, body weight, immunologic/lymphoreticular, and neurological effects (Anthony et al. 1986; Davies and Holub 1980a, 1980b; Earl et al. 1971; Enan et al. 1982; Lox and Davis 1983; Williams et al. 1959). Data from these studies sufficiently demonstrate that diazinon is an anticholinesterase insecticide. The adverse effects reported in humans and laboratory animals following exposure via inhalation, dermal, or oral routes are predominately cholinergic responses deriving from erythrocyte or neuromuscular and central nervous system inhibition of acetylcholinesterase: MRLs of 0.009 mg/m³ for inhalation exposure (Hartmann 1990) and 0.0002 mg/kg/day for oral exposure to diazinon (Barnes 1988) were derived from the database assembled for this profile. The MRLs are based on clear dose-response

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effects of diazinon on the target for diazinon toxicity, neural acetylcholinesterase. Further information on the dermal toxicity and toxicokinetics for all routes in both humans and laboratory animals would be helpful for use in the assessment of intermediate-duration exposure protective levels, especially for persons near hazardous waste sites or establishments where wastes containing diazinon are released into the air, or near agricultural establishments where diazinon is used regularly.

Chronic-Duration Exposure and Cancer. No adequate epidemiological studies regarding the potential carcinogenicity or systemic toxicity of diazinon resulting from chronic exposure in humans are available. Two adequate studies have been conducted with rats and mice (NCI 1979). While not designed as a cancer bioassay, in a recent study where rats (groups of 20-30) were orally exposed to diazinon (Kirchner 1991) for 98 weeks, histopathology of some 30-40 different tissues showed no treatment-related increase in neoplasms. 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 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 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 (presumed to be by several concurrent routes of exposure) studies. 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 that are 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

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exchange in peripheral blood lymphocytes in these individuals (de Ferrari et al. 1991; Kiraly et al. 1979; See et al. 1990). The results from these studies are confounded by either concurrent or sequential (or both) exposures to other unknown toxic substances, mainly other insecticides, that may be genotoxic. No *in vivo* genotoxicity studies in laboratory animals were located for diazinon. 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 ret-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. Only three animal studies on the reproductive effects of diazinon exposure were located. The first study in rats actually found that oral diazinon exposure increased litter size (Green 1970), although a second rat study reported significant reduction ($p < 0.05$) in litter size at oral maternal diazinon doses of 0.18 and 9 mg/kg/day (Spyker and Avery 1977). The third study, a 4-generation study which used only three dogs per sex, reported a dose-response testicular atrophy and arrested spermatogenesis in males in the fourth generation (Earl et al. 1971). Consequently, additional information on the reproductive effects in humans and animals is needed before the effect of diazinon exposure on human reproduction can be fully evaluated.

Developmental Toxicity. Information regarding the developmental effects in humans from exposure to diazinon was not located. Most of the located studies in laboratory animals did not find any significant developmental effects in the rats, mice, hamsters, and rabbits tested (Bamett et al. 1980; Green 1970; Robens 1969; Spyker and Avery 1977). In some of these studies, marked reduction in rat pup birth weight and continued significant retardation in growth rate (at 60 days,

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F₄ treated rats weighed approximately only 50% as much as controls) (Green 1970), and significantly elevated ($p < 0.05$) mortality in rat pups at weaning (Bamett et al. 1980) were reported. The 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 (Spyker and Avery 1977). Consequently, additional developmental studies in humans and animals by the inhalation and oral routes would be helpful in determining the human developmental toxicity of diazinon exposure.

Immunotoxicity. Autopsy reports in which the victims were exposed to high acute doses of diazinon described damage to immune structures (spleen, thymus) (Limaye 1966; Poklis et al. 1980). One 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). A dose-response splenic degeneration after 232 days of diazinon exposure was also reported in one dog study in which only three dogs per sex were used (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. In other laboratory studies, 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). Evidently, diazinon has shown a potential to induce immunologic/lymphoreticular responses in laboratory animals. Additional human studies with diazinon 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 acetylcholinesterase (Coye et al. 1987; Davies and Holub 1980a, 1980b; Edson and Noakes 1960; 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, as manifested by muscular fasciculations, weakness, and paralysis; mydriasis; tachycardia; hypertension; miosis; excessive glandular secretions

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(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 laboratory animal studies in 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. However, the diazinon exposure levels at which these neurological effects begin to occur in chronic oral and inhalation exposures in humans and laboratory animals are not known. Therefore, additional studies designed to quantify acute and chronic LOAELs in humans and laboratory animals would be helpful for use in the development of MRLs 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 or to lower concentrations for long periods.

Epidemiological and Human Dosimetry Studies. Available epidemiological studies sufficiently identify acetylcholinesterase inhibition as the characteristic and most critical effect from acute exposure to diazinon. However, these studies do not sufficiently identify the doses at which this effect occurs, although evidence from animal studies provides a measure of the lowest effect level (Coye et al. 1987; Davies and Holub 1980a, 1980b; Edson and Noakes 1960; Enan et al. 1982; Harris et al. 1969; Rajendra et al. 1986; Takahashi et al. 1991; Wecker et al. 1985). The results of an animal study indicated that more subtle effects of neuromuscular deficits in offspring of animals maternally exposed to doses lower than those that elicit acetylcholinesterase inhibition may be critical in assessing diazinon toxicity in humans. The authors of this animal study speculated that the mechanism of this reported effect is either indirect diazinon impairment of placental transport of nutrients or maternal regulation of fetal growth, or direct antagonism to cholinergic development of the fetus (Spyker and Avery 1977). The available epidemiological studies are inadequate for assessing the carcinogenic potential of this substance because the results from these studies are confounded by concurrent and/or sequential exposures to other potentially cancer-causing substances, mainly other insecticides (Cantor et al. 1992; Davis et al. 1993; Morris et al. 1986). These studies also lack adequate dose quantification. Additional chronic-duration oral, inhalation, and dermal studies would be helpful to

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determine the acute-duration lowest-effect level for acetylcholinesterase inhibition and the effect on offspring of low-dose maternal exposure to diazinon during gestation, and to provide unequivocal data about the carcinogenic potential of diazinon in humans. This information would be useful in assessing the human health consequences of short- and long-term oral, inhalation, or dermal exposure in specific populations, especially those living around hazardous waste sites or establishments where wastes containing diazinon are released into the air or water, and those that are occupationally exposed to diazinon for long periods of time.

Biomarkers of Exposure and Effect.

Exposure. Diazinon is rapidly adsorbed from the gastrointestinal tract and widely distributed throughout the body in both humans (Poklis et al. 1980) and animals (Janes et al. 1973; Mticke et al. 1970). 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 (Mticke 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 2-isopropyl-4-methyl-6-hydroxypyrimidine diethylphosphorothioic acid, and diethylphosphoric acid have been reported following oral exposure of animals to diazinon (Aizawa 1989; Iverson et al. 1975; Machin et al. 1975; Mount 1984; Mticke et al. 1970; Yang et al. 1971) while only diethylphosphorothioic acid and diethylphosphoric acid have been detected in the urine of exposed insecticide applicators (Maizlish et al. 1987). Although analysis of urine samples for the presence of these metabolites represents a potential means of assessing recent human exposure to diazinon, these metabolites can originate from exposure to other organophosphorus compounds and, therefore, are not specific for diazinon exposure. Additionally, these studies do not report a quantitative association between metabolite levels and exposure to diazinon in humans. Thus, these biomarkers are only indicative of exposure to diazinon (or other organophosphorus compounds) and are not specifically useful for diazinon exposure nor for dosimetric analysis. Further studies designed to refine the identification of metabolites specific to diazinon and provide dosimetric data will be useful in the search for a more dependable biomarker of diazinon exposure.

Effect. The major action resulting from human exposure to diazinon is the inhibition of acetylcholinesterase (Coye et al. 1987; Davies and Holub 1980a, 1980b; Edson and Noakes 1960; Enan et al. 1982; Harris et al. 1969; Rajendra et al. 1986; Takahashi et al. 1991; Wecker et al. 1985). Two

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pools of cholinesterases are present in human blood: acetylcholinesterase in erythrocytes and serum cholinesterase in plasma. Acetylcholinesterase, present in human erythrocytes, is identical to the enzyme present in neuromuscular tissue (the target of diazinon action). Inhibition of both forms of cholinesterase have been associated with exposure to diazinon in humans and animals (Coye et al. 1987; Edson and Noakes 1960; Soliman et al. 1982). While serum cholinesterase has no known physiological function, available data indicate that serum cholinesterase activity is a more sensitive marker for diazinon exposure than erythrocyte acetylcholinesterase activity (Endo et al. 1988; Hayes et al. 1980). Therefore, future studies that provide qualitative and dosimetric information regarding diazinon exposure and serum cholinesterase 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). Animal studies also confirmed 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; Mticke et al. 1970). Dermal absorption was estimated to be 34% of the applied dose with no difference related to the vehicle or to the area where it was applied in human volunteers dermally exposed for 24 hours to [¹⁴C]diazinon applied to either the forearm or abdomen in acetone or lanolin wool grease (Wester et al. 1993). Absorbed diazinon was rapidly and widely distributed to body tissues in humans (Poklis et al. 1980). Animal studies confirmed the observation in humans (Mticke et al. 1970), in sheep (Abdelsalam and Ford 1986; Janes et al. 1973; Machin et al. 1971, 1974). Absorbed diazinon is metabolized extensively. Several metabolites (monoethyl phosphate, diethyl phosphate, diethyl phosphorothioate) and small amounts of unchanged diazinon -were found in the serum and urine of suicide victims who ingested diazinon (Klemmer et al. 1978; Poklis et al. 1980). Complete degradation of the pyrimidine ring does not take place; however, the ethyl side chain was completely degraded as indicated by results of a study conducted in rats. Detection of 2-isopropyl-4-methyl-6-hydroxypyrimidine and its oxidation products (oxidation at the primary and tertiary carbon atoms of the isopropyl side chains) indicates that the main degradative mechanism of diazinon is the hydrolysis of its ester bonds by cytochrome P-450

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(Machin et al. 1975; Mucke et al. 1970). Diazinon is rapidly excreted in animals. Approximately 50-85% of diazinon doses were excreted, predominately via the urinary route, within 12-24 hours of dosing in animals. About 18-25% was excreted in the feces with a small amount expired in air (Iverson et al. 1975; Mount 1984; Miicke et al. 1970). Diazinon was not detected in the milk of lactating goats following oral administration (Mount 1984). Human volunteers excreted 34% of a dermally applied diazinon dose in the urine within 7 days (Wester et al. 1993). Additional studies in animals, designed to measure the rate of gastrointestinal absorption, 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 would be useful in assessing the toxicokinetics of diazinon in humans, especially those living around hazardous waste sites or establishments where wastes containing diazinon are released into the air or water, and those that are occupationally exposed to diazinon for long periods of time.

Comparative Toxicokinetics. Diazinon, an anticholinesterase organophosphate, inhibits acetylcholinesterase in the central and peripheral nervous system resulting in cholinergic symptoms, in some cases. This effect has been reported in several human studies (Coye et al. 1987; Kabrawala et al. 1965; Klemmer et al. 1978; Limaye 1966; Maizlish et al. 1987; Rayner et al. 1972; Richter et al. 1992; Stalberg et al. 1978). Laboratory animal studies have confirmed this characteristic toxicity of diazinon. These animals also exhibited acetylcholinesterase inhibition and cholinergic response, in some cases (Boyd and Carsky 1969; Davies and Holub 1980a, 1980b; Earl et al. 1971; Edson and Noakes 1960; Harris et al. 1969; Takahashi et al. 1991). Although cholinergic symptoms and acetylcholinesterase inhibition resulted from human inhalation and dermal exposures to diazinon (Coye et al. 1987; Lee 1989; Maizlish et al. 1987; Rayner et al. 1972; Richter et al. 1992; Soliman et al. 1982; Stalberg et al. 1978), no comparative animal studies are available. There is a correlation in the data regarding the absorption, distribution, metabolism, and excretion of diazinon following oral doses in both animal and human studies (Abdelsalam and Ford 1986; Iverson et al. 1975; Janes et al. 1973; Machin et al. 1971, 1974; Mount 1984; Miicke et al. 1970; Poklis et al. 1980); however, comparative data on the distribution and metabolism of diazinon after inhalation or dermal exposure in humans or animals, or on the excretion of diazinon after dermal exposure in animals are not available. Further studies are required to fill these data gaps.

Methods for Reducing Toxic Effects. Organophosphate insecticides like diazinon are rapidly absorbed and metabolized after inhalation, ingestion, and dermal contact (Iverson et al. 1975; Miicke et

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al. 1970). Consequently, efforts at reducing body burdens of poisoned persons may not be critical to the outcome. In oral exposures, emesis is not indicated because of the danger of aspiration of stomach contents by an obtunded patient. Methods suggested for removing gastrointestinal tract diazinon content include gastric lavage and administration of activated charcoal (Shankar 1967, 1978). Cathartics are considered unnecessary. Dialysis and hemoperfusion are not indicated in organophosphate poisonings because of the extensive tissue distribution of the absorbed doses (Miicke et al. 1970; Poklis et al. 1980). In dermal or ocular exposures, thorough decontamination including discarding of contaminated clothing, copious washing of affected body parts with soap and water, and irrigation of the eyes with saline are recommended. Moving of victims to fresh air, airway suctioning, endotracheal intubation, and artificial ventilation with supplemental oxygen are recommended for inhalation exposures. Timely treatment of diazinon poisoning cases with atropine and 2-PAM significantly reduces the cholinergic effects (Harris et al. 1969; Klemmer et al. 1978; Shankar 1967, 1978). Atropine is an anti-muscarinic agent which, in large doses, alleviates bronchoconstriction and reduces secretion in the oral cavity and the airway induced by diazinon poisoning. Atropine also counters some of the central nervous system effects (Woo 1990). 2-PAM is given to regenerate inhibited cholinesterase (acetylcholinesterase) enzyme at all affected sites (Schenker et al. 1992; Shankar 1967, 1978). The available information sufficiently satisfies the need for methods of reducing toxic effects. Therefore, further studies in this regard are not required.

2.10.3 Ongoing Studies

The combined toxicity of cimetidine (the active ingredient in the anti-ulcer drug Tagamet) and the insecticide diazinon is being investigated in a study at the National Institute of Environmental Health Sciences in an effort to determine if simultaneous exposure to these two compounds might enhance the toxicity of diazinon. Results of these studies indicate that diazinon is very rapidly metabolized and that simultaneous exposure to cimetidine has little effect on the half-life of diazinon but does alter the ratio of some metabolites formed.

The Occupational Studies Section of the National Cancer Institute, Division of Cancer Etiology, is currently conducting epidemiologic studies to identify and quantify occupational causes of cancer. During the past year, investigations have uncovered associations between employment as a farmer and lymphatic and hematopoietic, skin, lip, brain, stomach, and prostate cancer. Use of several insecticides

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including diazinon was linked with non-Hodgkin's lymphoma. Occupational groups with complex exposures under study include farmers and insecticide applicators.

The U.S. Department of Agriculture is sponsoring several studies on diazinon. The University of Minnesota is developing and maintaining a network of information resources on the uses, benefits, and hazards of insecticides placed under

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of diazinon is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of diazinon is located in Table 3-2.

3. CHEMICAL AND PHYSICAL INFORMATION

Table 3-1. Chemical Identity of Diazinon

Characteristic	Information	Reference
Chemical name	Phosphorothioic acid, 0,0-diethyl-O-(2-isopropyl- 6-methyl-4-pyrimidinyl) ester	HSDB 1996; ASTER 1995
Synonym(s)	O,O-Diethyl-O-(2-isopropyl-4- methyl-6-pyrimidinyl) phosphorothionate; 0,0-diethyl-O-[6-methyl-2-(1- methylethyl)-4-pyrimidinyl] phosphorothioate; others	HSDB 1996
Registered trade name(s)	Diazinon, Alfa-tox, Basudin, Diazol, AG 500, Garden Tox, Knox-out, Spectracide, others	HSDB 1996 Merck 1989
Chemical formula	$C_{12}H_{21}N_2O_3PS$	HSDB 1996
Chemical structure		Merck 1989
Identification numbers:		
CAS registry	333-41-5	HSDB 1996
NIOSH RTECS	TF 3325000	HSDB 1996
EPA hazardous waste	No data	
OHM-TADS	7216512	HSDB 1996
DOT/UN/NA/IMCO shipping	NA2783 Diazinon; IM06.3 Organophosphorous pesticides; UN 2783 Organophosphorous pesticides;	HSDB 1996
HSDB	303	HSDB 1996
NCI	CO 8673	HSDB 1996

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

3. CHEMICAL AND PHYSICAL INFORMATION

Table 3-2. Physical and Chemical Properties of Diazinon

Property	Information	Reference
Molecular weight	304.36	Merck 1989
Color	Colorless	HSDB 1996
Physical state	Liquid	Merck 1989
Melting point	No data	
Boiling point	83–84 °C at 2×10^{-3} mm Hg Decomposes at >120 °C 85–90 °C at 0.05 mm Hg	Merck 1989 Weast and Astle 1985
Density at 20 °C/4 °C	1.116–1.118 g/mL 1.1088 g/mL	Merck 1989 Weast and Astel 1985
Odor	Faint ester-like	Merck 1989
Odor threshold:		
Water	No data	
Air	No data	
Taste threshold	No data	
Solubility:		
Water at 20 °C	0.004% (40 mg/L) 68.8 mg/L 51.8 mg/L (Calculated)	Merck 1989 Howard 1991 ASTER 1995
Organic solvent(s)	Miscible with petroleum ether, alcohols, ether, cyclohexane, benzene and similar hydrocarbons	Merck 1989
Partition coefficients:		
Log K_{ow}	3.81	Howard 1991
Log K_{oc}	1.602–2.635, avg. 2.281 2.515 clay loam 2.243 high clay	HSDB 1996
Vapor pressure at 20 °C	1.4×10^{-4} mm Hg 8.4×10^{-5} mm Hg	Merck 1989 Howard 1991
at 40 °C	1.1×10^{-3} mm Hg	Merck 1989
Henry's law constant (no temperature data provided)	1.4×10^{-6} atm-m ³ /mol 1.13×10^{-7} atm-m ³ /mol 2.79×10^{-9} atm-m ³ /mol	HSDB 1996 Howard 1991 ASTER 1995
Autoignition temperature	No data	
Flash point	No data	
Flammability limits	Practically nonflammable	HSDB 1996
Conversion factors		
ppm (mole:mole) to mg/m ³ in air (25 °C)	1 ppm = 12.4 mg/m ³	Calculated
mg/m ³ to ppm (mole:mole) in air (25 °C)	1 mg/m ³ = 0.0806 ppm	
Explosive limits	No data	

HSDB = Hazardous Substances Data Base

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

4.1 PRODUCTION

Diazinon is the Ciba-Geigy Corporation trademark name for the active ingredient O,O-diethyl-0-(2-[1-methylethyl]-4-methyl-6-pyrimidinyl) phosphorothioate. This insecticide is produced commercially by reacting 2-isopropyl-4-hydroxy-6-methylpyrimidine and O,O-diethyl phosphorochloridothioate (HSDB 1996). 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 and by SureCo Inc. in Fort Valley, Georgia (SRI 1995).

Estimated diazinon production in the United States for 1982 was 2.63 million kg (5.8 million pounds) (HSDB 1996). 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).

No current information is available from the Toxics Release Inventory database on facilities that manufacture or process diazinon, the intended use, or the range of maximum amounts of diazinon that are stored on-site because diazinon was not one of the chemicals that facilities were required to report (EPA 1995a, 1995b). Beginning on January 1, 1995, however, 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) (EPA 1995b). Although no production and use data are currently available, information for 1995 should be available in the TR195 database listing in 1997.

4.2 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 1996). 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.

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

Little quantitative information was found on either past or current volumes of diazinon exported from the United States. With respect to exports, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) generally prohibits the EPA from releasing complete information on pesticide production, sales, and distribution (FASE 1996). In a recent 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). Thus, export volumes for diazinon for 1992, 1993 and 1994 could actually be four times higher than the export volume identified (FASE 1996). Data on past and/or current export volumes are not adequate to assess trends in export volumes of this pesticide.

4.3 USE

Diazinon is an organophosphate pesticide which was first registered for use in the United States in 1956 (EPA 1990b). It was first developed as a nonsystemic insecticide and nematocide for use against soil insects and pests of fruit trees and vineyards, vegetables (e.g., corn, potatoes), rice, sugarcane, forage, range, pasture, grasslands, tobacco, and horticultural crops (Farm Chemicals Handbook 1993; Worthing and Walker 1983). Diazinon is used to control flies around refuse storage areas and in fair grounds, zoos, animal facilities, or other businesses and public places where food or animal wastes might accumulate (Anonymous 1989; Williams et al. 1985). 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 livestock to control biting insects or skin parasites and in pet collars to control ticks in veterinary applications (EPA 1990b; 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 is heavily used in urban areas (Farm Chemicals Handbook 1993). It is used extensively in home and garden applications and in formulations designed to prevent such pests as crickets or

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

cockroaches from infesting homes or offices. It is commonly used in the form of pest control strips around entry ways (Jackson and Lewis 1981) and is often sprayed in offices as a general purpose fumigant (Currie et al. 1990). It was 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). Various types of diazinon formulations are produced including dusts, emulsifiable concentrates, granules, impregnated materials, microencapsulated forms, pressurized sprays, soluble concentrates, and wettable powders (EPA 1990b).

Estimated diazinon use in the United States was 2.6 million pounds (1.18 million kg) of active ingredient for 1983 (Gianessi 1986) and 10 million pounds (4.5 million kg) of active ingredient for 1985 (EPA 1990b). It was estimated that up to 43% of the diazinon applied in this country in 1982 was for non-agricultural uses, 21% was used on field crops (e.g., peanuts, rice, sugarcane, small grains, and citrus), 12% on alfalfa, 5% on corn, 5% on soybeans, 5% on vegetables, 3% on fruit and nut trees, 2% on wheat, 2% on cotton, and 2% on sorghum (HSDB 1996). More recent information on applications for this pesticide was not located.

4.4 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 7).

Diazinon undergoes rapid chemical hydrolysis under both alkaline and acid conditions. Alkaline hydrolysis results in complete degradation of diazinon to the alkaline salt of diethylthiophosphoric acid and 2-isopropyl-4-methyl-6-hydroxypyrimidine, which are considerably less toxic than diazinon. Acid hydrolysis in the presence of excess water results in the same hydrolysis products as in alkaline hydrolysis. However, with insufficient water in the acid medium, highly toxic tetraethykdithio- and thiopyrophosphates have been produced. Residuals were once acidified and then discharged or soil applied, with the addition of water for dilution. Without careful controls, the direct acid hydrolysis of diazinon can produce a variety of products, many of which are equal to or exceed the toxicity of the original active ingredient (HSDB 1996; IRPTC 1985; Sovocool et al. 1981). For ultimate disposal, large amounts of diazinon residuals should be incinerated in a unit with effluent gas scrubbing, while

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controlled hydrolysis or innovative bioremediation techniques may be appropriate for disposal of smaller quantities of diazinon (IRPTC 1985).

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.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Diazinon is released to the environment solely by human activities. Major atmospheric emissions result from volatilization of the chemical from soil resulting from its use as a soil nematocide and 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. No current information is available on total environmental releases of diazinon from production and processing facilities to air, water, and soil because these facilities were not required to report releases to the Toxics Release Inventory until January 1, 1995 (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. Diazinon has been detected in the atmosphere and trace amounts of its oxygen analogue (diazoxon) have also been detected. The oxon to thion ratio ranged from 0.056 to 7.1, but was generally less than 0.4 (Glotfelty et al. 1990a). In a study of diazinon use in the Central Valley of California, Seiber et al. (1993) reported that during daylight hours, the oxon to thion ratio in the atmosphere averaged 0.52, while at night the ratio was 0.10. Diazinon can be converted to diazoxon in the atmosphere via ultraviolet radiation (UV) (Aizawa 1989). The estimated half-life for the vapor phase reaction of diazinon with hydroxyl radicals is approximately 4 hours (SRC 1995). Diazinon can be transported moderate distances in the air from its original point of use (Zabik and Seiber 1993).

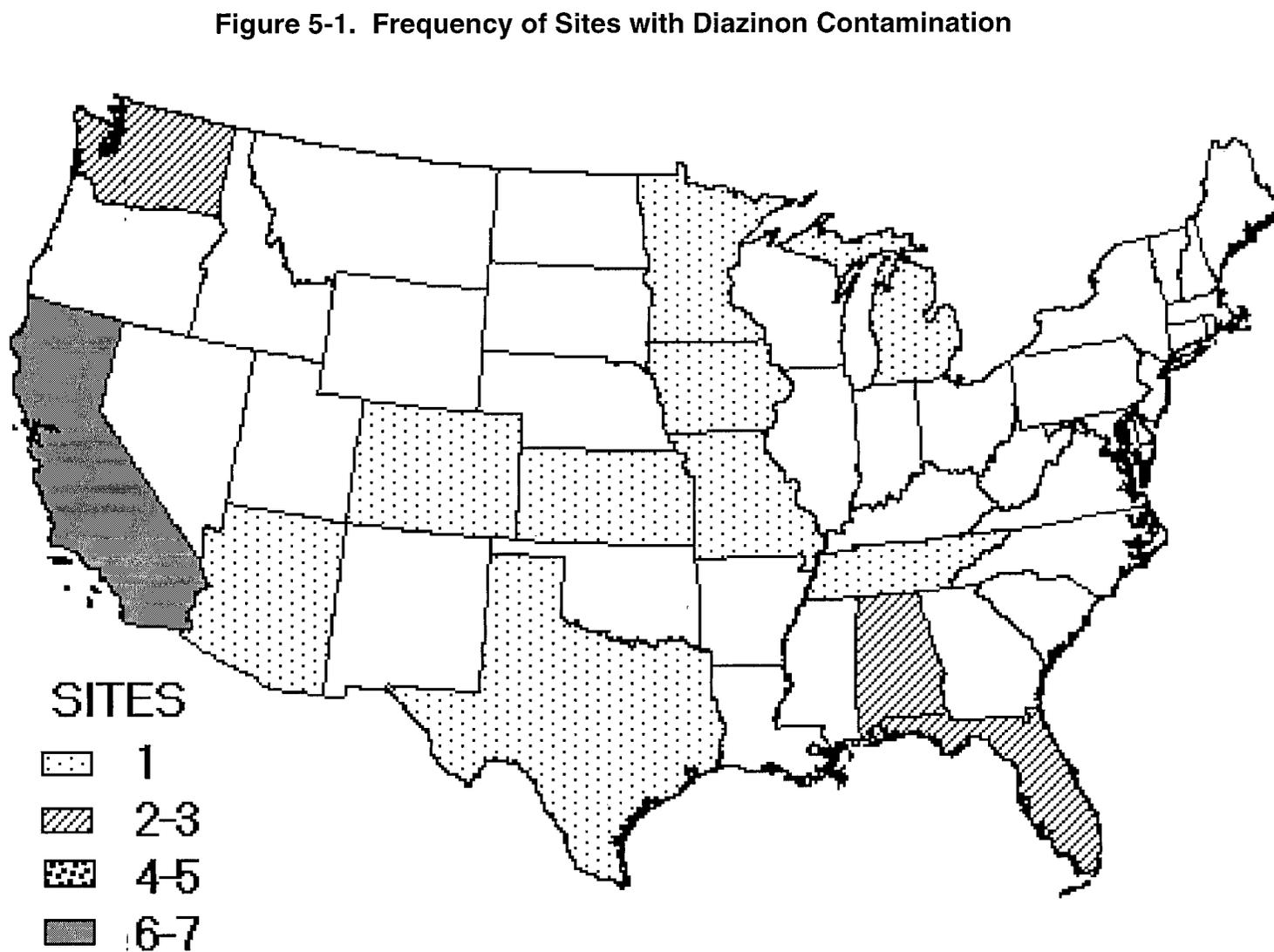
Diazinon released to surface waters or soil is subject to volatilization, photolysis, hydrolysis, and biodegradation. Biodegradation, primarily under aerobic conditions, is a major fate process for diazinon associated with water and soil. Diazinon can be biodegraded under anaerobic conditions as well. 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, and sunlight as well as the presence of microorganisms (Chapman and Cole 1982; Ferrando et al. 1992; Frank et al. 1991b; Scheunert et al. 1993; Schoen and Winterlin 1987; Sharom et al. 1980b; Wolfe et al. 1976). 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 less than 3%, and can leach from soil into groundwater. If released to water, this pesticide does not bioaccumulate (BCF values generally less than 100) in aquatic organisms.

In the United States, monitoring efforts under many national programs have not analyzed for this chemical. In addition, environmental monitoring efforts in general have decreased noticeably within the last decade. This makes it difficult to provide current quantitative estimates on the fate and transport of diazinon in various environmental compartments. 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 is still widely used, with many applications in urban areas (homes and gardens) that increase the possibilities of human exposure. Diazinon and its major metabolite, diazoxon, have significant acute toxicity to humans. The predominant exposure pathway for the general population appears to be via dermal exposure during application of the compound for commercial and domestic pest control uses and via inhalation in indoor air spaces during or immediately following application. Dermal exposure is probably a more significant exposure of people using the pesticide for home and garden applications. Exposure to diazinon can also result from ingestion of contaminated food and water. Exposure is greatest for those individuals occupationally exposed to diazinon, particularly those involved in its production and manufacture; those involved in its application for agricultural, commercial, or domestic pest control uses; and those involved in its disposal at hazardous waste sites.

Diazinon has been identified in at least 18 of the 1,430 current or former EPA National Priorities List (NPL) hazardous waste sites (HazDat 1996). However, the number of sites evaluated for diazinon is not known. The frequency of these sites within the United States can be seen in Figure 5-1.



Derived from HazDat 1996

5. POTENTIAL FOR HUMAN EXPOSURE

5.2 RELEASES TO THE ENVIRONMENT

Prior to January 1, 1995, facilities involved in the production or processing of diazinon were not required to report the amount of releases to various environmental matrices (EPA 1995a, 1995b). Data on diazinon releases for 1995 will be available in the Toxics Release Inventory database in 1997.

Diazinon has been identified in a variety of environmental media (surface water, leachate, groundwater, soil and sediment) collected at at least 18 of the 1,430 current or former EPA National Priorities (NPL) hazardous waste sites where diazinon was detected in some environmental media (HazDat 1996).

5.2.1 Air

Diazinon is released into the atmosphere solely by human activities associated with its production and use as a pesticide. These releases include releases to ambient air from production, and from agricultural or 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. Volatilization from the home and garden applications that now may account for over 40% of total diazinon usage is impossible to estimate.

No information was available in the Toxics Release Inventory database on releases of diazinon to air from manufacturing and processing facilities because these facilities were not required to report releases of this chemical prior to January 1, 1995 (EPA 1995a, 1995b).

Diazinon has not been identified in air samples collected at any of the 18 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 1996).

5.2.2 Water

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. Since diazinon is not

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a Priority Pollutant under the Clean Water Act, it has not been evaluated extensively in water quality monitoring programs in rivers, lakes, or estuaries. Recently 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 widespread use of diazinon in 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; Kuivila 1993; Maguire and Tkacz 1993; Szeto et al. 1990; 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 (Kuivila 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 (9 ppt). Contaminated water samples collected from the San Joaquin River produced 100% mortality in bioassay tests conducted with *Cerioduphnia 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 (Kuivila 1993).

No information was available in the Toxics Release Inventory database on releases of diazinon to water from manufacturing or processing facilities because these facilities were not required to report releases of this chemical prior to January 1, 1995 (EPA 1995a, 1995b).

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 1989a). In areas with heavy applications of diazinon combined with irrigation or water-level adjustment techniques, diazinon detections in groundwater also have been

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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 identified in surface water, leachate, and groundwater samples collected at 4, 1, and 9 of the current or former NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 1996).

5.2.3 Soil

Diazinon is released into soils primarily from its registered use on various agricultural crops and its 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 Kuivula 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. The absence of current statistics on pesticide production, sales, and/or usage make it difficult to estimate releases to soils or sediments.

No information was available in the Toxics Release Inventory database on releases of diazinon to soil from manufacturing and processing facilities because these facilities were not required to report releases of this chemical prior to January 1, 1995 (EPA 1995a, 1995b).

Diazinon has been identified in top soil samples (<3 inches deep), subsurface samples (>3 inches deep), soil samples with unspecified depth, and in sediment samples collected at 4, 2, 4, and 4 current or former NPL hazardous waste sites, respectively, where diazinon was detected in some environmental media (HazDat 1996).

5.3 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.

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5.3.1 Transport and Partitioning

Based on its vapor pressure (see Table 3-2), if diazinon is released to the atmosphere, it will be expected to exist both in the vapor phase and particulate phase (Eisenreich et al. 1981). Glotfelty et al. (1990a) reported that during stagnant inversion fog events in the Central Valley of California, 56% and 19% of the diazinon in the air-phase was associated with vapor and aerosol particles, respectively, and only 24% of the diazinon was dissolved in the water phase. Schomburg et al. (1991) reported slightly different distributions for fog events resulting from advected oceanic fog. In this study, 26% and 10% of the diazinon in the air-phase was associated with vapor and aerosol particles, respectively; 62% of the diazinon was dissolved in the water phase. Zabik and Seiber (1993) studied the atmospheric transport of diazinon from California's Central Valley to the Sierra Nevada Mountains. These samples collected during January through February 1991 represented the simultaneous collection of both vapor and particulate phases. Concentrations of diazinon and its oxon ranged from 13 to 10,000 pg/m³ and 4 to 3,000 pg/m³, respectively, for samples collected at the 114 m elevation and from 1.4 to 12 pg/m³ and 1.8 to 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 diazinon oxon.

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 (thiono to oxon 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 evaporation may not be expected to be significant based upon the Henry's law constant (see Table 3-2), volatilization of diazinon can be an important transport process. Sanders and Seiber (1983) reported

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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 biological concentrations factor (BCF) values obtained for various freshwater and saltwater fish and invertebrate species is presented in Table 5-1. 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 researchers still recommend caution in consuming some aquatic species (EPA 1993; Keizer et al. 1991). This is in large measure because the mechanisms that fish and invertebrates use to metabolize diazinon are poorly understood and seem to vary widely from species to species. In addition, diazinon and its metabolites have not been widely monitored in aquatic species. Since some of the metabolites of diazinon are themselves toxic, a measure of caution may still be in order in cases where there is reason to believe edible fish or shellfish have had recent exposure to diazinon (Keizer et al. 1991). This is partially the basis for the EPA recommendation to states to consider routine monitoring for diazinon in edible fish and shellfish species as part of their state toxics monitoring programs particularly in those watersheds where extensive use of diazinon is identified (EPA 1993).

Diazinon released in soil from its registered uses partitions to the atmosphere through volatilization, to surface water via runoff, and to groundwater as a result of leaching. According to Kenaga (1980), chemical compounds with an K_{oc} of <100 are considered moderately to highly mobile; diazinon with a K_{oc} value of 40-432 (mean of 191), therefore, would be considered moderately mobile. Additional parameters influencing the leaching potential of this chemical include the soil type (e.g., clay versus sand), the amount of rainfall, the depth of the groundwater, and the extent of degradation. In laboratory tests of sand and organic soil, Sharom et al. (1980a) found that 26, 22, 11, 11, and 7% of the diazinon leached from sand (after 5 successive 200 mL rinses), respectively. A total of 95% of the diazinon added to the sand leached after 10 successive 200 mL rinses. In organic soil, however, only 3, 4, 11, 9, and 7% of the diazinon leached from soil (after 5 successive 200 mL rinses), respectively. Only 50% of diazinon added to the organic soil leached after 10 successive 200 mL rinses. While

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Table 5-1. Bioconcentration Data for Diazinon

Species common name Scientific name	Exposure type	Duration (days)	BCF ^a	Reference
<u>Freshwater</u>				
Shrimp <i>Paratya compressa compressa</i>	F	3	4	Seguchi and Asaka 1981
Oriental weatherfish <i>Misgurnus anguilli candatus</i>	F	14	28	Seguchi and Asaka 1981
Common carp <i>Cyprinus carpio</i>	F	3	130	Seguchi and Asaka 1981
Perch <i>Sarotherodon galilaeus</i>	S	3	39	El Arab et al. 1990
Rainbow trout <i>Oncorhynchus mykiss</i>	F	3	92	Seguchi and Asaka 1981
Brook trout <i>Salvelinus fontinalis</i>	F	210	25	EPA 1977
Guppy <i>Poecilia reticulata</i>	R	2	39	Keizer et al. 1991
Zebra fish <i>Brachydanio rerio</i>	R	2	300	Keizer et al. 1991
Willow Shiner <i>Gnathopogon caerulescens</i>	F	7	248	Tsuda et al. 1989
Killifish <i>Oryzias latipes</i>	F	3	20	Tsuda et al. 1995
Fathead minnow <i>Pimephales promelas</i>	F	2–304	337 ^b	Veith and Kosian 1983
<u>Saltwater</u>				
Sheepshead minnow <i>Cyprinodon variegatus</i>	F	108	147	Goodman et al. 1979

^aBCF listed is the highest BCF value reported in the cited reference.

^bCalculated quantitative structure-activity relationship (QSAR) value as reported in ASTER.

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

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diazinon can show sorption in soils with high organic content (>3%), in most other soil types diazinon has properties suggesting a moderate potential for leaching into groundwater (Arienzo et al. 1994; Sharom et al. 1980a). Arienzo et al. (1994) tested the adsorption and mobility of diazinon in 25 soils with different physicochemical properties. Diazinon was found to be slightly mobile in 80% of the soils tested (those with organic matter content <3%), and immobile in 20% of the soils tested (those with organic matter content >3%). The compound leached primarily from light soils with low organic matter content. Levanon et al. (1994) assessed the impact of plow tillage on microbial activity and the fate of diazinon and other pesticides in the top 5 cm soil layer. A higher leaching rate for diazinon was detected in plow tillage soils than in no-tillage soils after incubation for 21 days. The no-tillage soils were characterized by a higher organic matter content and higher microbial populations and activity than the plow tillage soils.

Arienzo et al. (1993) conducted a study of adsorption and mobility of diazinon in soils from aqueous media and mixtures of methanol-water and hexane-water. Adsorption of diazinon by soils from aqueous systems was related to organic matter content (i.e., the higher the organic content, the greater the adsorption). In methanol-water and hexane-water systems, the adsorption of diazinon by soils decreased. This situation may arise at hazardous waste disposal sites where pesticide waste residues and cosolvents may be encountered together. The presence of these organic solvents will increase the mobility (leachability) of diazinon in the soil and increase the potential for groundwater contamination. Diazinon has been detected in groundwater in the United States (Cohen 1986; EPA 1989a; HazDat 1996), and in the Great Lakes region of Ontario, Canada (Frank et al. 1987, 1990b).

5.3.2 Transformation and Degradation

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

5.3.2.1 Air

Diazinon, once released to the atmosphere, may be subject to direct photolysis since it absorbs light in the spectra above 290 nm (Gore et al. 1971). Glotfelty et al. (1990a), Schomburg et al. (1991), Seiber et al. (1993), and Zabik and Seiber (1993), all reported the presence of diazinon and its activated product (diazoxon) in atmospheric samples. Glotfelty et al. (1990a) believe that diazoxon is formed

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by atmospheric oxidation especially during the daylight hours. Schomburg et al. (1991) reported that diazinon undergoes transformation to diazoxon during atmospheric transport from agricultural to nonagricultural areas. Seiber et al. (1993) reported mean concentrations of diazinon of 76.8 ng/m³ and of diazoxon of 10.8 ng/m³ in air samples collected near fruit and nut orchards in Parlier, California. The half-life (first-order kinetics) for the vapor phase reaction of diazinon with hydroxyl radicals in the atmosphere is estimated to be 4 hours, assuming an atmosphere containing 5x10⁵ hydroxyl radicals/m³ at 25 °C (SRC 1995).

5.3.2.2 Water

Diazinon released to water may be subject to both abiotic degradation (i.e., hydrolysis and photolysis) and biotic degradation by microorganisms. The rate of abiotic degradation is influenced strongly by pH and temperature. In a laboratory study, Chapman and Cole (1982) reported that pH alone influenced the half-life of diazinon maintained in sterile water-ethanol (99:1) phosphate buffer solutions at 25 °C. Degradation of diazinon was most rapid under acidic conditions with half-life values in weeks (days shown in parentheses) (first-order kinetics) of 0.45 (3.15), 2.0 (14), 7.8 (54.6), 10.0 (70), and 7.7 (53.9) at pH values of 4.5, 5.0, 6.0, 7.0, and 8.0, respectively. Garcia-Repetto et al. (1994) also studied the influence of pH on the degradation of diazinon in water-ethanol (9: 1) solutions maintained between 15 and 31 °C. These authors reported estimated half-life values (first-order kinetics) for diazinon of 1.31, 8.57, and 8.19 days at pH values of 2, 7.5, and 8.7, respectively. The higher temperatures and lower pH conditions of this study may account for the more rapid degradation rates. Frank et al. (1991b) followed the degradation of diazinon in natural surface/groundwater samples at pH 8.2 that were either stored in the laboratory at 4 °C in the dark or at 21 °C under ambient indoor fluorescent light conditions for 125 days. Under the two temperature and light regimes the half-life values (first-order kinetics) of diazinon were 14 days (light at 21 °C) and 45 days (dark at 4 °C). Degradation was more affected by temperature suggesting that hydrolysis was the primary mode of degradation.

Wolfe et al. (1976) reported that diazinon absorbs sunlight less than some of its organophosphate relatives, but that diazinon undergoes direct photolysis in water. The estimated half-life (first-order kinetics) for photolysis in aqueous solutions maintained in glass cells and irradiated with a mercury vapor lamp (>290 nm) was 1,000 hours (42 days). Frank et al. (1991b) investigated the degradation of diazinon in surface and groundwater samples, but found little difference in the rate of diazinon

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degradation in light and dark conditions. The half-life (first-order kinetics) of diazinon of 88 days (light) and 99 days (dark) suggests that photolysis was not a major factor in degradation.

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

Sharom et al. (1980b) studied the degradation of diazinon under laboratory conditions using both distilled water and natural water samples. Degradation was more rapid in natural water (pH 7.7) (12 weeks) than in sterilized natural water, sterilized distilled water, or distilled water (>16 weeks), suggesting that biodegradation of diazinon was occurring. Ferrando et al. (1992) conducted a laboratory microcosm study using both natural surface water and tap water. These experiments were conducted in aerated aquaria, maintained at 22 °C 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 hours 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.

Although diazinon has been detected in groundwater samples in both the United States and Canada (Cohen 1986; EPA 1989a; Frank et al. 1987, 1990b; HazDat 1996), 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).

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5.3.2.3 Soil Transformation and Degradation

Once released to soils and sediments, diazinon can be degraded by hydrolysis, photolysis, and biodegradation by several genera of microorganisms. Microbial degradation appears to be the major pathway for the degradation of diazinon in soils; however, under anaerobic conditions, abiotic hydrolysis appears to be the most probable mechanism responsible for degradation of the compound under acidic soil conditions (EPA 1990b).

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

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

In a study of degradation of diazinon in three submerged tropical soils, only 2-6% of the originally applied diazinon remained 50-70 days postapplication (Sethunathan and MacRae 1969). Degradation of diazinon was more rapid in nonsterilized soils, indicating microbial participation in two of the three

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soil types. In the third type (an acid clay soil), diazinon degradation was more rapid in the sterilized samples at pH 4.7, apparently because of the compound's instability under acid conditions.

Streptomyces sp. isolated from the submerged soils could degrade the diazinon. In a field study of a treated cranberry bog by Szeto et al. (1990), disappearance of diazinon from irrigation ditch sediment (pH 4.4) and from sediment in an adjacent reservoir (pH 5.0) was equally rapid. These authors found that less than 1% of diazinon remained 38 and 22 days postapplication in the irrigation ditch and reservoir sediments, respectively. In nonsterilized soil, diazinon degradation was faster at 100% water saturation than at 50% water saturation. These results suggest that microbial activity under anaerobic conditions plays an important role in diazinon degradation (Schoen and Winterlin 1987).

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

Gunner and Zuckerman (1968) reported synergistic microbial degradation of diazinon by two microorganisms, *Arthrobacter sp.* and *Streptomyces sp.* When *Arthrobacter sp.* and *Streptomyces sp.* were incubated separately on growth media where diazinon was the primary carbon source, neither was able to convert the pyrimidinyl carbon to carbon dioxide. When incubated together, only 6% of the parent diazinon remained, and 94% was converted to two unidentified metabolites. Two microorganisms isolated from flood soils also were found to hydrolyze diazinon (Adhya et al. 1981). Diazinon was rapidly hydrolyzed within 24 hours by both *Flavobacterium sp.* and *Pseudomonas sp.* A hydrolysis product of diazinon, 2-isopropyl-6-methyl-4-hydroxypyrimidine, was metabolized more rapidly by the *Flavobacterium sp.* than the *Pseudomonas sp.* More recently, oxypyrimidine was reported to be the major soil degradation product of diazinon and is considered to be more persistent than diazinon (EPA 1990b). Barik and Munnecke (1982) reported that an enzyme (parathion hydrolase) obtained from *Pseudomonas sp.* cultures could hydrolyze diazinon in soils. More than 98% of 10,000 ppm of diazinon in soil can be degraded within 24 hours if sufficient buffer and enzyme are added to the contaminated soil. The authors report that it is technically feasible to use parathion hydrolase to clean up diazinon spills in the environment.

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

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Most information on diazinon concentrations in various environmental media derived from large scale monitoring networks dates from before the mid-1980s and no longer reflects current conditions. There is a noticeable lack of national monitoring studies that would allow meaningful estimation of current diazinon concentrations associated with various environmental media. Reliable evaluation of the potential for human exposure to diazinon depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on diazinon levels monitored in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

5.4.1 Air

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

In a study of pesticide residues in ambient air sampled in 14-16 states during 1970, 1971, and 1972, diazinon was detected in 50% of the 2,479 samples analyzed, with a mean concentration of 2.5 ng/m³ and a maximum concentration of 62.2 ng/m³ (Kutz et al. 1976). Carey and Kutz (1985) reported that

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ambient air concentrations of diazinon collected from February through September 1980 in Perkin, Illinois, ranged from 1.3 to 10 ng/m³.

In a study of pesticide levels in ambient suburban air, diazinon was detected in 80, 80, and 40% of samples collected in three cities (Miami, Florida; Jackson, Mississippi; and Fort Collins, Colorado), respectively. The maximum diazinon concentration detected in each city was 3.9, 2.0, and 2.2 ng/m³ for Miami, Florida; Jackson, Mississippi; and Fort Collins, Colorado, respectively (Kutz et al. 1976). During 1973-1974, diazinon concentrations in air were measured in urban Miami, Florida, and in the adjacent Everglades National Park. Urban diazinon levels ranged from not detectable to 3.3 ng/m³ (1.5 ng/m³ mean); corresponding levels in Everglades National Park ranged from not detectable to 1.9 ng/m³ (0.6 ng/m³ mean) (Lewis and Lee 1976). Nationwide, diazinon was detected in 48% of 123 urban air samples collected in ten U.S. cities during 1980. The maximum diazinon concentration reported was 23 ng/m³ (mean 2.1 ng/m³) (Carey and Kutz 1985).

Most recently, non-occupational exposure to diazinon among residents of two U.S. cities (Jacksonville, Florida, and Springfield, Massachusetts) was studied over three seasons: summer 1986, spring 1987, and winter 1988 (Whitmore et al. 1994). The study focused primarily on inhalation exposures with primary environmental monitoring consisting of 24-hour indoor and outdoor air. For the Jacksonville, Florida, population, the estimated mean diazinon concentrations ranged from 85.7 to 420.7 ng/m³ in indoor air and 1.1 to 13.8 ng/m³ in outdoor air. For the Springfield, Massachusetts, population, mean exposures were much less. The estimated diazinon concentrations ranged from 2.5 to 48.4 ng/m³ in indoor air and 8.2 to 9.2 ng/m³ in outdoor air.

Ambient diazinon concentrations were measured under foggy atmospheric conditions in and around the Central Valley of California (Parlier, California), which is a prime agricultural area dominated by fruit, nut, and citrus orchards (Glotfelty et al. 1990a; Seiber et al. 1993; Zabik and Seiber 1993). In fog, diazinon concentration was 1.6 ng/m³ and diazoxon (the oxon transformation product) concentration was 0.82 ng/m³. In a similar study, Schomburg et al. (1991) analyzed air and fog near Monterey, California, to determine whether the uptake of diazinon in advected oceanic fog was different from uptake in fog collected under stagnant inversion conditions in the Central Valley of California. Fog water concentrations of diazinon ranged from 0.15 to 4.8 µg/L (ppb) in coastal areas; higher concentrations ranging from 0.3 to 18 µg/L (ppb) were found in the Central Valley area. Diazinon and diazoxon favored the aqueous phase in foggy atmosphere, with 62.4 and 87.8%, respectively,

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reported in the aqueous phase. Zabik and Seiber (1993) studied the atmospheric transport of diazinon from California's Central Valley to the Sierra Nevada Mountains. Air samples collected from January through February 1991 represented the simultaneous collection of both vapor and particulate phases. Concentrations of diazinon and its oxon ranged from 13 to 10,000 pg/m^3 (0.013-10 ng/m^3) and 4 to 3,000 pg/m^3 (0.004-3 ng/m^3), respectively, for samples collected at the 114 m elevation and from 1.4 to 12 pg/m^3 (0.0014-0.012 ng/m^3) and 1.8 to 13 pg/m^3 (0.0018-0.013 ng/m^3), respectively, at the 533 m elevation. The pesticide concentrations in air samples decreased with distance and elevation moving east from the Central Valley into the higher elevations of the Sierra Nevada Mountains. At times, air concentrations of diazinon at the 114 m elevation were 1,000 times greater than concentrations detected at 533 m elevation. Concentrations at the 1,920 m elevation were typically below the limit of quantification. Wet deposition samples (rain and snow) collected at the 114 m elevation contained up to 6,100 pg/mL (6.1 ppb) diazinon and 2,300 pg/mL (2.3 ppb) diazoxon.

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

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

Diazinon air concentrations related to vapors released from pest control strips were measured by Jackson and Lewis (1981). Diazinon levels in indoor air increased from 0.32 $\mu\text{g}/\text{m}^3$ at 6 hours after

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application of the pest strips to $1.34 \mu\text{g}/\text{m}^3$ on day 15, and then declined to $1.21 \mu\text{g}/\text{m}^3$ on day 30. Air sampling in a retail garden store where pesticide containers with diazinon were displayed showed an average diazinon concentration of $3.4 \mu\text{g}/\text{m}^3$ (Wachs et al. 1983).

Currie et al. (1990) evaluated the concentrations of diazinon in indoor air and on working surfaces for a period of 10 days after application in commercial offices. The highest concentrations of diazinon (163 and $158 \text{ yg}/\text{m}^3$) were measured 4 hours postapplication in two empty offices, while the concentration in the furnished office was $27 \mu\text{g}/\text{m}^3$. One day postapplication, levels were 125 and $70 \mu\text{g}/\text{m}^3$ in the two empty offices and $27 \mu\text{g}/\text{m}^3$ in the furnished office. Air concentrations of diazinon continued to decline and on day 6 postapplication were approximately $3.5 \mu\text{g}/\text{m}^3$ in the empty offices and $8 \mu\text{g}/\text{m}^3$ in the furnished office. Airborne levels of diazinon were distinctly lower in the furnished office, and this was attributed to obstruction of the applicator's spraying path by office furniture so that a lower amount of diazinon was applied. Diazinon deposition on aluminum plates was measured as an indicator of surface contamination, measurements ranged from 0.4 - $15 \text{ ng}/\text{cm}^2$. No overall decrease in surface contamination occurred over time. Plates suspended 1.5 - 2.1 m above the floor generally exhibited higher diazinon levels 24 hours post-treatment than at 1 - 2 hours posttreatment. The authors believe this was a result of evaporation of diazinon from the carpeted floor augmented by air turbulence. Diazinon contamination measured by surface wipes on furniture and foil on carpet ranged from 13 to $38 \text{ ng}/\text{cm}^2$.

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

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Lenhart and Kawamoto (1994) reported air concentrations of up to 297 $\mu\text{g}/\text{m}^3$ in greenhouse air after spray applications of an emulsifiable concentrate of diazinon (Clean Crop AG500), and concentrations up to 3,030 $\mu\text{g}/\text{m}^3$ in greenhouse air after a 4-hour cold fogging application of the same formulation.

Palmgren and Lee (1984) collected samples of grain dust (dust accumulated in the dust collection systems of grain elevators) from six grain elevators located in the New Orleans, Louisiana, area to evaluate potential occupational exposures of grain elevator personnel. Diazinon concentrations in grain dust were $<0.01 \mu\text{g}/\text{g}$ for all 31 samples collected. The authors concluded that the concentration of diazinon on the grain dust posed no hazard.

5.4.2 Water

Since diazinon is not a priority pollutant and has not been considered to pose serious threats from bioconcentration or bioaccumulation in fish and shellfish species, it has attracted far less attention in the United States than persistent organochlorines like DDT or chlordane in routine surface water monitoring networks. Carey and Kutz (1985) reported that the maximum diazinon residue collected in a national surface water monitoring program conducted from 1976 to 1980 was 2.38 ppb and that diazinon was detected in only 1.2% of the samples collected. More recently, Pereira and Hostettler (1993) conducted a study of the Mississippi River and its tributaries during 1991 and 1992. These authors reported that diazinon was detected in water samples from the Illinois River at concentrations of 20 ng/L (0.02 ppb) and from several sites on the mainstem of the lower Mississippi River at concentrations ranging from 4 to 10 ng/L (0.004-0.010 ppb). During 1991, Domagalski and Kuivila (1993) monitored diazinon concentrations in water and suspended sediment collected at various sites in San Francisco Bay during low river discharge and after spring rain events. Diazinon was detected in water only after the spring rains and most (98%) of the diazinon was in the dissolved phase. Concentrations dissolved in the water column ranged from 4.6 to 14.6 ng/L (0.005-0.015 ppb). The authors suggest that diazinon may be close to equilibrium with respect to sorption or desorption on suspended sediment particles.

In the Great Lakes region, diazinon was detected in surface waters in several river basins in southern Ontario, Canada. Braun and Frank (1980) monitored surface water concentrations of 8 organochlorine and 12 organophosphate pesticides in 11 agricultural watersheds in southern Ontario. All watersheds drained into the Great Lakes. Diazinon residues as a result of field use were detected in only one

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water shed, but the chemical was repeatedly detected in 34% of samples (1975-76) and 74% of samples (1976-77) collected from one creek. The source of the diazinon was traced to its indoor use to control flies in a series of mushroom houses that discharged via a drainage tile system directly to the creek. The maximum residues of diazinon in the stream were 140 ppb (5.75 ppb mean) and 26 ppb (1.02 ppb mean) in 1975-76 and 1976-77, respectively. In a more recent study, Frank and Logan (1988) measured pesticide and industrial chemical residues at the mouth of the Grand, Saugeen, and Thames Rivers in southern Ontario, Canada, from 1981 through 1985. River water samples collected at the mouths of the three rivers (that drain into the Great Lakes) were analyzed for 20 herbicides, 3 fungicides, and 25 insecticides including diazinon. One water sample collected during May through August 1982 contained a mean diazinon concentration of 0.21 ppb. Maguire and Tkacz (1993) monitored concentration of pesticides in surface water near the mouths of the Yamaska River in Quebec, Canada, and five of its tributaries during 1986 and 1987. Diazinon was detected at the mouth of the Yamaska River at concentrations ranging from 2.1 to 11.9 ng/L (0.002-0.012 ppb), at the mouth of the Saint-Nazaire River at concentrations ranging from 3.1 to 26.7 ng/L (0.003-0.027 ppb), and at the mouth of the Salvail River at concentrations ranging from 1.1 to 4.9 ng/L (0.001-0.005 ppb). Frank et al. (1990a) conducted a survey of 211 rural ponds in southern Ontario and measured concentrations of 29 herbicides, fungicides, and insecticides including diazinon. Two ponds were found to be contaminated with diazinon, and residues in pond water ranged from 0.6 to 1.7 ppb (1.2 ± 0.8 ppb mean). The source of the diazinon in these two cases was attributed to accidental pesticide spills during agricultural application.

Diazinon concentrations in water have also been monitored in the United States and in several Canadian studies associated with the use of the compound in agricultural applications. Kendall et al. (1993) monitored diazinon residues in ponds and creeks adjacent to a golf course in coastal Washington where two turf applications of diazinon were made at a rate of 2.2 kg active ingredient per hectare. A maximum diazinon residue of 17 ppb was measured in the study area ponds and creeks. Wan et al. (1994) monitored concentrations of diazinon and six other organophosphate pesticides in farm ditches of the lower Fraser River Valley of British Columbia, Canada, from July to December 1991. These authors reported that diazinon was consistently found in ditch water (81% of samples) at 7 locations with a mean concentration of 0.07 $\mu\text{g/L}$ (ppb) (range of 0.01-0.34 $\mu\text{g/L}$ [ppb]). The percentage of positive detections for diazinon in water samples was 81%. The presence of diazinon in ditch water was correlated with consistent detection of diazinon residues in soils from nearby fields. Szeto et al. (1990) monitored the persistence of diazinon in coastal cranberry bogs and

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adjacent surface waters in British Columbia, Canada. Bogs were treated with two applications of diazinon 5G (granules) at a rate of 6 kg active ingredient per hectare approximately 2 weeks apart. One day after the first and second applications, maximum concentrations of diazinon in water in an irrigation ditch were 338 ppb and 456 ppb, respectively. Maximum concentrations in an adjacent reservoir were 78.5 ppb and 58.1 ppb for the first and second treatments, respectively. Water samples collected immediately outside the diked bog area contained a maximum of 29.1 ppb diazinon, but concentrations were usually <10 ppb. Tributary water 100 m downstream from the cranberry bog site contained a maximum diazinon residue of 2.8 ppb.

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

In a groundwater contamination study of 28 of California's 58 counties that evaluated over 50 pesticides (from both point and nonpoint sources), diazinon was detected in 12 samples (Cohen 1986). Diazinon is included as an analyte of interest in the EPA Pesticides in Ground Water Database (EPA 1989a) and was detected at two sites. A detection in California was related to point source contamination (residue level was unspecified), and a detection of 478 ppb (maximum) and 162 ppb (mean) in Mississippi was in an area where appreciable agricultural use of pesticides occurs. In the Great Lakes region, diazinon was found in a survey of rural wells in southern Ontario, Canada, monitored between 1979 and 1984 (Frank et al. 1987) and in farm wells monitored between 1986 and 1987 (Frank et al. 1990b). However, no concentrations of diazinon in groundwater were provided by these authors.

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5.4.3 Sediment and Soil

Diazinon has not been the focus of many national soil or sediment monitoring programs in the United States, but has been monitored in regional studies associated with agricultural applications in both the United States and Canada. In a national surface water quality monitoring study (1976-1980), diazinon was detected in 0.5% of the sediment samples analyzed, with a maximum residue of 7.1 ppb (Carey and Kutz 1985). Domagalski and Kiuivila (1993) reported concentrations of diazinon in suspended sediments from various sites from San Francisco Bay ranging from not detected to 2.8 ng/g (ppb).

Soil contamination of diazinon ranging from 95.5 mg/m² (2 hours postapplication) to 35.6 mg/m² (342 hours postapplication) resulted from spray applications of 4.5 kg diazinon (50 WP formulation) per hectare to a dormant peach orchard in the Central Valley of California (Glotfelty et al. 1990b). Diazinon concentrations in sediments of a cranberry bog treated with two applications of diazinon (Diazinon 5G at 6 kg active ingredient per hectare) were measured by Szeto et al. (1990). These authors reported that the highest diazinon residues were 21 ppm (21,000 ppb) (wet weight) in sediments of irrigation ditches collected 4 days postapplication. The maximum sediment concentration measured in an adjacent reservoir was 2 ppm (2,000 ppb). Four days postapplication, the maximum sediment concentration was 80 ppb in a waterway outside the diked bog and only 10 ppb in a tributary 100 meters downstream from the bog. Wan et al. (1994) monitored ditch water, soils, and sediments from July to December 1991 in an agricultural area in the lower Fraser River Valley of British Columbia, Canada. Diazinon concentrations in ditch sediment were detected at three sites; the mean concentrations were 8, 2, and 38 µg/kg (ppb) at the Vancouver, Cloverdale, and Sumas Prairie sites, respectively. Diazinon was also detected in topsoil (<5 cm deep) at five sites; the mean concentrations were 268 µg/kg (268 ppb) (range of 2-3,307 µg/kg), 5 µg/kg (ppb) (range of 1-9 µg/kg), 769 µg/kg (ppb) (range of 13-2862 µg/kg), 13 µg/kg (ppb) (range of 4-30 µg/kg), and 39 µg/kg (ppb) (range of 1-236 µg/kg) at the Westham Island, Ladner, Bumaby, Cloverdale, and Sumas Prairie sites, respectively. The concentrations at all these stations declined from July to December.

5.4.4 Other Environmental Media

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

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maximum diazinon concentrations measured in the contaminated creek water for 1975-76 and 1976-77 were 140 ppb (5.75 ppb mean) and 26 ppb (1.02 ppb mean), respectively.

Pesticide residue data in domestic and imported foods and animal feeds from 1982 to 1986 were evaluated by Hundley et al. (1988). These authors reported that diazinon was detected in a wide variety of domestic foods: garbanzo beans, green beans, pinkos dry beans, broccoli, celery, limes, collards, cucumbers, endives, butter lettuce, green leaf lettuce, iceberg lettuce, watermelons, green onions, parsley, Chinese peas, spinach, Italian squash, Swiss chard, and tomatoes. None of the samples exceeded EPA tolerance limits. Diazinon was also detected in the following imported foods: apples, broccoli, dried cherries, cucumbers, feijoa, kiwi fruit, green leaf lettuce, red leaf lettuce, romaine lettuce, cantaloupe, okra, green onions, Chinese peas, Anaheim peppers, bell peppers, caribe peppers, jalapeno peppers, serano peppers, prunes, raisins, Italian squash, yellow squash, and tomatoes. Only residues in caribe peppers exceeded the EPA tolerance limit. Concentrations of diazinon in ready-to-eat foods were monitored for 10 years from 1982 to 1991 through the FDA's Revised Market Basket Survey (KAN-DO Office and Pesticide Teams 1995). Diazinon was detected in 894 samples of 144 different foods at a mean concentration of 0.0019 $\mu\text{g/g}$ (1.9 ppb).

The frequency of detection of diazinon in the FDA Total Diet Study conducted from 1982 to 1984 was 13% (Gunderson 1988). Diazinon intakes, in $\mu\text{g/kg}$ body weight/day, estimated for these total diet analyses (1982-1984) were 0.0121, 0.0129, and 0.0073 for 6-11-month-old infants, 14-16-year-old males, and 60-65-year-old females, respectively. More recently, the frequency of occurrence of diazinon detections in the FDA Total Diet Study declined to 9% in 1989 (FDA 1990), 6% in 1990 (FDA 1991), 4% in 1991 (FDA 1992), 5% from 1991 to 1993 (FDA 1994), and 5% in 1994 (FDA 1995). Diazinon intakes in $\mu\text{g/kg}$ body weight/day, estimated for the total diet analyses also declined from intakes estimated in the 1982-84 analysis and were 0.0031, 0.0034, and 0.0017 in 1989 (FDA 1990); 0.0026, 0.0022, and 0.0017 in 1990 (FDA 1991); and 0.0049, 0.0022, and 0.0022 in 1991 (FDA 1992) for 6-11-month-old infants, 14-16-year-old-males, and 60-65-year-old-females, respectively.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

While no quantitative information is available on the percentage of diazinon released to each environmental compartment, diazinon can be emitted to any or all environmental media (air, surface

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water, groundwater, and soil) depending on the source of the release, formulation used, and prevailing environmental conditions. General population exposure to diazinon may occur through three routes: dermal contact, inhalation, and ingestion of contaminated food or drinking water. The major routes of exposure to diazinon for the general population are through dermal contact directly with the chemical during domestic application for control of home and garden pests; through dermal contact with diazinon-treated plant materials such as grass clippings; or through dermal contact with treated surfaces (e.g., furniture) in domestic or office buildings. For children particularly, a potential source of exposure can be related to the indoor application of diazinon on furniture, rugs, and flooring. The general population may also be exposed to diazinon through inhalation of contaminated ambient (outdoor) air particularly in agricultural areas where diazinon is extensively used or in urban areas where it is applied to lawns and gardens. Since many commercial buildings and residential buildings are sprayed with diazinon or use pest control strips that vaporize diazinon, there is the possibility of exposure from inhalation of vapors in these diazinon-treated indoor air spaces. The oral route of exposure may include ingestion of foods contaminated with small residues of diazinon or consumption of contaminated drinking water.

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

Non-occupational exposure to diazinon for residents of two U.S. cities (Jacksonville, Florida, and Springfield, Massachusetts) were studied over three seasons: summer 1986, spring 1987, and winter 1988 (Whitmore et al. 1994). The study focused primarily on inhalation exposures with primary environmental monitoring consisting of 24-hour indoor air, personal air, and outdoor air. For the population of Jacksonville, Florida, the mean diazinon concentration ranges were 85.7-42.0.7 ng/m^3 for indoor air, 1.1-13.8 ng/m^3 for outdoor air, and 89.0-321.6 ng/m^3 for personal air. For the population in Springfield, Massachusetts, mean exposures were much less. The diazinon concentrations were 2.548.4 ng/m^3 for indoor air, 8.2-9.2 ng/m^3 for outdoor air, and 1.4-10.1 ng/m^3 for personal air. The mean air exposure for diazinon in Jacksonville, Florida, was 1,380 ng/day , and dietary exposures were 590-1,140 ng/day . The mean air exposure estimated for Springfield, Massachusetts, was almost

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10 times lower (158 ng/day), while the dietary exposure (586 ng/day) was equal to the low end of the range for the population of Jacksonville, Florida. In Jacksonville, Florida, characterized as a high pesticide use area, inhalation exposure exceeded dietary exposure; in Springfield, Massachusetts, characterized as a low pesticide use area, the dietary exposure to diazinon exceeded the inhalation exposure.

Workers employed in industries that manufacture, formulate, package, or apply diazinon and workers involved in the disposal of diazinon or diazinon-containing wastes have the potential to be exposed to the highest concentrations of diazinon. In occupational settings, dermal exposure and subsequent absorption through intact skin is the most important route of exposure, and inhalation exposure is generally less important (Jeyaratnam and Maroni 1994). Inhalation of diazinon depends on its volatility, the type of formulation used, and the application technique employed. Occupational ingestion may occur as a result of poor work practices and/or lack of personal hygiene.

NIOSH recommends that the occupational exposure level not exceed $100 \mu\text{g}/\text{m}^3$ for a 10-hour TWA workday (NIOSH 1992). In addition, the American Conference of Governmental Industrial Hygienists has recommended a time-weighted average threshold limit value (TWA-TLV) of $100 \mu\text{g}/\text{m}^3$ for occupational exposure to diazinon (ACGIH 1986).

Except for professional pesticide applicators or farm workers, the exposure risks from diazinon appear relatively minor as long as label instructions are followed and safeguards are taken to avoid extensive dermal contact. Even studies of dermal exposure typical of shearers handling sheep that have been dipped in diazinon showed dermal absorption rates of less than 4% (Wester et al. 1993). Studies of dermal exposure for workers in grain elevators failed to detect diazinon in grain dust above the $0.01 \mu\text{g}/\text{g}$ detection limit, although much higher levels have been reported from Australia (Palmgren and Lee 1984).

The use of a 2-day lag period from the time of diazinon application to the use of office or domestic indoor space appears adequate to eliminate exposure risks from vapors and residues that might be incurred from either inhalation or dermal absorption. Air sampling of a room treated with 36 pest control strips measured a maximum diazinon air concentration of $1.34 \mu\text{g}/\text{m}^3$ 15 days postapplication (Jackson and Lewis 1981). Similarly, Williams et al. (1987) found that air sampling in two animal facility areas used by facility personnel and treated monthly with a 1% aqueous diazinon solution

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measured 2-3 $\mu\text{g}/\text{m}^3$ less than 24 hours postapplication. Currie et al. (1990) also measured diazinon air concentrations in empty and furnished offices treated with a 1% aqueous solution. Four hours postapplication, diazinon air concentrations were 163 and 158 $\mu\text{g}/\text{m}^3$ in two empty offices and 28 $\mu\text{g}/\text{m}^3$ in the furnished office. One day postapplication, diazinon levels in the offices ranged from 125 $\mu\text{g}/\text{m}^3$ (empty office) to 27 $\mu\text{g}/\text{m}^3$ (furnished office), but by 2 days postapplication the highest diazinon air concentration measured was 53 $\mu\text{g}/\text{m}^3$. Air sampling levels of diazinon 2 days posttreatment in these three indoor exposure contexts were well below the NIOSH 8-hour TWA permissible exposure level (PEL) of 100 $\mu\text{g}/\text{m}^3$.

Residual air concentrations of diazinon in a commercial greenhouse were studied by Lenhart and Kawamoto (1994). These authors monitored diazinon air concentrations applied as a spray and by cold fogging. The 40 minute spray application was made to a portion of the greenhouse with only passive ventilation (adjustable window vents). During application, circulating fans were turned off and all roof vents were closed. After the spray application, 1.4 L of the diazinon emulsifiable concentrate formulation in 18 L of water were added to each of two cold fogging machines set for a 4-hour cold fogging application. Air samples were collected during the work shift prior to pesticide application, hourly during the application, and for 4 consecutive days after the pesticide application. Full shift area air samples were collected. During the postapplication period, air circulating fans were continuously operated and the roof vents were open occasionally. The 8-hour TWA for the spray application ranged from not detected to 25 $\mu\text{g}/\text{m}^3$. The 8 hour TWA diazinon concentrations ranged from 6.0 to 52 $\mu\text{g}/\text{m}^3$ (Saturday), 3 to 30 $\mu\text{g}/\text{m}^3$ (Sunday), 2.4 to 17 $\mu\text{g}/\text{m}^3$ (Monday), and not detected to 12 $\mu\text{g}/\text{m}^3$ (Tuesday). During the cold fogging application, diazinon concentrations on Friday ranged from 730 to 3,030 $\mu\text{g}/\text{m}^3$. Residual 8-hour TWA concentrations for this application ranged from 70 to 250 $\mu\text{g}/\text{m}^3$ (Saturday), 27 to 67 $\mu\text{g}/\text{m}^3$ (Sunday), 20 to 59 $\mu\text{g}/\text{m}^3$ (Monday), and 19 to 40 $\mu\text{g}/\text{m}^3$ (Tuesday). Two of the 4 samples collected on Saturday exceeded the NIOSH TWA permissible exposure level of 100 $\mu\text{g}/\text{m}^3$ for occupational exposures to diazinon. Results of this study indicate that greenhouse workers can be at risk of inhalation exposure to residual diazinon concentrations. The authors believe that all diazinon applications should be conducted on Friday evenings after the greenhouse workers have left so that much of the residual pesticide can settle over the weekend.

Finally, air sampling at a retail garden store conducted to determine exposures for retail employees showed levels of diazinon averaging only 3.4 $\mu\text{g}/\text{m}^3$, well below the NIOSH TWA exposure level of 100 $\mu\text{g}/\text{m}^3$ (Wachs et al. 1983). However, these authors point out that the air concentrations they

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reported may vary greatly among retail stores depending on the amounts and types of diazinon formulation sold, air temperature, condition of the packaging material (e.g., tom packaging, loose lids), prior spills, and types of floor coverings.

The National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that 39,342 workers (including 3,216 women) employed at 3,168 facilities were potentially exposed to diazinon in the United States (NOES 1990). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

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

5.7 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 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.

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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.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. While the principal properties of diazinon are well characterized, (ASTER 1995; Howard 1991; HSDB 1996; Merck 1989) there are data gaps for melting point, odor and taste thresholds, autoignition temperature, flash point, and explosive limits for the compound. Additional information on these properties would be helpful in assessing the compound's environmental fate. There are also data gaps for some spontaneously-produced degradation products some of which may be as toxic or more toxic than diazinon.

Production, Import/Export, Use, Release, and Disposal. As with many pesticide agents, limited current information was found on production, import and export volumes, or even on registered use patterns for diazinon. No information was available from the Toxics Release Inventory on facilities involved in the production or processing of diazinon because it was not one of the chemicals the facilities were required to report prior to January 1, 1995 (EPA 1995a, 1995b). This lack of information seriously compromises efforts to design monitoring programs to study fate and transport and can seriously jeopardize proper assessments of exposure opportunities and health risks for this compound.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1995, will become available in May of 1997. This database will be updated yearly and should provide a list of industrial - - production facilities and emissions.

Environmental Fate. Diazinon is moderately mobile in some soil types (Arienzo et al. 1994; Kenaga 1980; Sharom et al. 1980a). Information on the mobility of diazinon and on a major degradation product 2-isopropyl-6-methyl-4-hydroxypyrimidine in various soil types is available

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(Arienzo et al. 1994; Levanon et al. 1994; Sharom et al. 1980a; Somasundaram et al. 1991). In the atmosphere, diazinon is subject to degradation due to photolysis (Gore et al. 1971) and reactions with hydroxyl radicals (Glotfelty et al. 1990a; Schomberg et al. 1991; Seiber et al. 1993; SRC 1995). In water, diazinon is subject to hydrolysis, photolysis and biodegradation. The rate of degradation of diazinon in water and soil is strongly influenced by pH (Chapman and Cole 1982; Ferrando et al. 1992; Frank et al. 1991b; Garcia-Repetto et al. 1994; Sharom et al. 1980b). Diazinon undergoes only slight photolysis in water, with reported half-life estimates ranging from 42 to 88 days (Frank et al. 1991b; Wolfe et al. 1976). Diazinon can be degraded at the soil surface by photolysis (Burkhard and Guth 1979), and in soils and sediment by hydrolysis (Chapman and Cole 1982; Levanon et al. 1994; Schoen and Winterlin 1987; Sethunathan and MacRae 1969; Somasundaram et al. 1989, 1991) and by biodegradation by microorganisms (Adhya et al. 1981; Batik and Munnecke 1982; Gunner and Zuckerman 1968). Additional information on the mechanism by which diazinon is converted to diazoxon in the atmosphere would be useful; additional information on the persistence and mobility of the major degradation products of diazinon would also be useful in evaluating the environmental fate of diazinon and its degradation products.

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

Food Chain Bioaccumulation. Diazinon has an estimated low bioconcentration potential (BCF=77) (Kenaga 1980) in aquatic organisms, which is generally confirmed by measured BCF values obtained from laboratory studies with fish and other aquatic invertebrates (El Arab et al. 1990; Keizer et al. 1991; Sancho et al. 1993; Tsuda et al. 1989, 1995). Further information on measured BCF values for additional edible fish and shellfish would be helpful, as would information on tissue residues of diazinon and its major degradation products in edible species. No information was found on studies associated with plant uptake, but diazinon is rarely detected above EPA tolerance limits

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(Hundley et al. 1988). Bioaccumulation in aquatic food chains does not appear to be important, and no further information on biomagnification is required.

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

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

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

Exposure Registries. No exposure registries for diazinon were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure

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Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.7.2 Ongoing Studies

The U.S. Department of Agriculture has sponsored several studies on diazinon.

Drs. G.K. Felton, W.W. Frye, and W. Witt at the University of Kentucky are studying the impact of agricultural systems on surface and groundwater quality. Research and management oriented catchment scale water quality models are being developed to describe the movement of pesticides and nutrients from soils into surface and groundwater. Two watersheds will be instrumented for continuous flow data collection and periodic water quality sampling (including data on diazinon). One watershed will be evaluated for chemical impacts on a mixed agriculture-forest-suburban watershed. The second watershed will be evaluated for chemical impacts due to shifts in land use.

The effects of floods on the removal of pesticide residues and nutrients from flooded areas used in cranberry production are being studied at the University of Massachusetts. Weekly water samples taken during the growing season will be analyzed to determine residues of diazinon, among other pesticides, near the flood gates of two cranberry bogs, in two conveying streams, and in three receiving waterbodies. Specimens of several edible shellfish species including blue crabs, scallops, and quahogs will also be analyzed for residues.

Dr. J.N. Seiber at the Range Wildlife and Forestry Department of the University of Nevada is studying the aerial transport and deposition of organophosphate insecticides including diazinon in Sierra Nevada forests. This study involves 1) developing methods for analyzing toxicants in air and atmospheric moisture; 2) determining concentrations and frequency of airborne residues of pesticides, conversion products, and other organic toxicants; 3) determining wet and dry deposition levels of toxicants in the Sierra Nevada and Great Basin areas; and 4) correlating the information with data on emissions, meteorology, physicochemical properties, and modeling. Pine needles from Ponderosa pines will be sampled to determine their ability to capture airborne pesticide residues.

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Dr. P. Jeffers at the State University of New York at Cortland is gathering information to determine the persistence of organophosphorus compounds in groundwater and the effects of various soils on the degradation and transport of these compounds. Both neutral and base hydrolysis processes will be evaluated. Transport studies in soil columns will be conducted to determine the mobility of diazinon in soils.

At the Agricultural Research Service in Raleigh, North Carolina, investigations are underway by Dr. D.E. Moreland to 1) characterize and elucidate the oxidation of endogenous and exogenous substrates including diazinon by plant cytochrome P-450 monooxygenases; and 2) identify treatments that stimulate the metabolism of diazinon and other pesticides, and lower pesticide residues in consumable agricultural plant products.

Dr. R.J. Wright at the Beltsville Agricultural Research Center, Beltsville, Maryland, is developing experimental approaches to allow direct measurement of pesticides including diazinon in wet and dry atmospheric deposition. The spatial and temporal distribution of airborne pesticide inputs to Chesapeake Bay will be determined to test predictive models of the atmospheric transport and deposition of agricultural chemicals.

Dr. A. Shaw at the University of Maryland Eastern Shore in Princess Anne, Maryland, is evaluating textile substrate for pesticide barrier effectiveness and comfort. Tests will be conducted to assess effectiveness of decontamination processes for these personal protection devices. Diazinon emulsifiable concentrates will be used to contaminate fabrics. Simulated wear studies will be conducted in the laboratory to assess the efficacy of these fabrics in protecting human health.

The U.S. Department of the Interior has also sponsored a study. Dr. C. Childress of the Department of the Interior, U.S. Geological Survey is conducting a surface water quality assessment for Region J, North Carolina. The purpose of this project is to gather long-term regional water-quality monitoring data for stream tributaries to the region's drinking water supplies. Many of these streams receive a complex combination of treated industrial and municipal effluents, in addition to nonpoint source urban and agricultural runoff. This project will supplement the existing state database for major ions, nutrients, and trace metals and create a new database on synthetic organic chemicals (e.g., diazinon). The purpose of this project is to 1) document spatial differences in regional surface water quality, 2) examine temporal trends in water quality, and 3) provide water quality data to local environmental

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planners and managers. The project will establish a fixed-interval monitoring network to assess water quality at 21 stream and 12 reservoir sites. Preliminary sampling has detected lindane, diazinon and/or dieldrin in nearly 50% of the water samples.

No additional information was located on current studies that would fill existing data needs for diazinon (FEDRIP 1995).

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring diazinon, its metabolites, and other biomarkers of exposure and effect to diazinon. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

In the design of a study and the selection of an analytical method, it is very important that adequate attention be paid to the extent of validation and field applicability of a particular method. Not all of the methods have been validated to the same extent. It is the analyst's responsibility to determine the data quality needed before initiating the application of a particular method.

The analytical methods used to quantify diazinon in biological and environmental samples are summarized below. Table 6-1 lists the applicable analytical methods for determining diazinon in biological fluids and tissues and Table 6-2 lists the methods used for determining diazinon in environmental samples.

6.1 BIOLOGICAL SAMPLES

Diazinon is widely used for agricultural purposes, and residues on or in foods can result in exposure of humans by ingestion. Additional exposure potentials exist as a result of home gardening activities. Consequently, methods for the determination of diazinon in biological samples can be used to verify that exposure and absorption have occurred. Since diazinon is rapidly metabolized, determination of the parent compound can provide evidence only of very recent exposures (see Chapter 2). Methods have been reported for metabolites, and these are discussed below under Biomarkers of Exposure. A few papers were found that deal with the determination of diazinon in human samples and these are described below. Some methods have reported the determination of diazinon in animal tissue or other

Table 6-1. Analytical Methods for Determining Diazinon and Transformation Products in Biological Samples

Sample matrix ^a	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human fatty tissue (from greater omentum)	Tissue pulverization and extraction with acetone. Concentration and purification by sweep co-distillation and Florisil/anhydrous sodium sulfate column chromatography. Elution with 20% ether in hexane followed by hexane. Addition of internal standard.	GC/NPD	No data	No data	Kirkbride 1987
Human adipose, bile, blood, brain, stomach contents, kidney, and liver	Maceration of 0.5 g sample in tissue grinder with acetonitrile. Addition of aqueous sodium sulfate and partitioning into hexane. Concentration and clean up using Florisil column.	GC/ECD; GC/FID	No data	No data	Poklis et al. 1980
Human urine (DEP, DETP)	Dilution of urine with acetonitrile, azeotropic distillation for water removal, evaporation of solvent, redissolution in acetone and derivatization using pentafluorobenzyl bromide.	GC/FPD	DEP: 0.072 ppm; DETP: 0.041 ppm	DEP: 96 (4.7% RSD); DETP: 99 (2.4% RSD) at 0.8 ppm.	Reid and Watts 1981
Dog urine (2-isopropyl-4-methyl-6-hydroxypyrimidine; 2-1'-hydroxy-1'-methyl)-ethyl-4-methyl-6-hydroxypyrimidine)	Extraction with chloroform, volume reduction, alkylation or silylation	GC/electrolytic conductivity detection	< 1 ppm	No data	Lawrence and Iverson 1975

Table 6-1. Analytical Methods for Determining Diazinon and Transformation Products in Biological Samples (continued)

Sample matrix ^a	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Bovine liver, rumen content (partially digested grain and vegetation mixture)	Extraction of homogenized sample with methanol-dichloromethane (10–90, v/v) followed by gel permeation chromatography and silica gel solid phase extraction clean-up.	GC/FPD	0.01–0.05 µ/g using 5 g sample	Rumen content: 95 (3% RSD) at 0.1 µg/g; liver: 88 (5% RSD) at 0.05 µg/g	Holstege et al. 1991
Avian liver, kidney	Homogenization with HCl/ethanol/ethyl acetate, centrifugation and evaporation of supernatant to dryness. Redissolution in hexane, filtration and clean up using GPC and volume reduction.	GC/FPD; GC/MS	0.02 ppm	100 (3% RSD) from liver at 0.5 µg/g (0.5 ppm)	Richardson and Sieber 1993
Animal fat	Sweep codistillation, Florisil clean up-elution with methylene chloride-light petroleum-acetonitrile (50+48.5+1.5)	GC/FPD	No data	90 (6% RSD) at 0.4 mg/kg	Brown et al. 1987

^a Diazinon is the target analytes unless otherwise specified.

DEP = O,O-Diethyl phosphate; DETP = O,O-Diethyl phosphorothionate; ECD = electron capture detector; FPD = flame photometric detector; GC = gas chromatography; GPC = gel permeation chromatography; MS = mass spectrometry; NPD = nitrogen phosphorus detector

Table 6-2. Analytical Methods for Determining Diazinon and Transformation Products in Environmental Samples

Sample matrix ^a	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air, gloves (surrogate for dermal exposure)	Preconcentration from air sample using polyurethane foam (PUF). Soxhlet extraction of PUF or gloves with 5% ethyl ether/hexane. Addition of deuterated internal standards and concentration using K-D and nitrogen blowdown.	Capillary GC/MS (can use multiple ion detection)	55 ng/m ³ (5.5 m ³ sample)	73 (14% RSD)	Hsu et al. 1988
Air (diazinon, diazoxon)	Preconcentration using ORBO-42 pesticide adsorbent tubes (Supelco). Extraction with acetone, evaporation just to dryness and redissolution in 100 µL acetone containing internal standard.	Capillary GC/NPD	No data	≥90 at 0.1 and 1 µg/m ³ (diazinon)	Williams et al. 1987
Air	Preconcentration of pesticide onto OVS-2 tube (13 mm quartz filter, XAD-2, 270 mg/140 mg. Elution with 90% toluene/10% acetone.	GC/FPD (NIOSH Method 5600)	0.0004 mg/m ³ (400 ng/m ³) for 120 L sample.	94 (2.7% RSD at 2.4 µg (0.01 µg/m ³ , 240 L sample)	NIOSH 1994
Air	Preconcentration of diazinon from air onto activated carbon fiber filter. Elution with benzene:ethanol (4:1 volume:volume) followed by volume reduction.	GC/MS	0.5 ng/m ³	95 ± 4.7% at 10 L/min sampling flow, 31 °C and 85 relative humidity	Kawata and Yasuhara 1994
Drinking water	Preconcentration onto 5 µm C ₁₈ -silica or 7 µm polystyrene-divinyl benzene copolymer with subsequent backflush onto analytical HPLC column.	RP-HPLC/UV (254 nm)	0.03–0.06 µg/L (ppb)	91 (±10% RSD) at sample volumes up to 300 mL	Driss et al. 1993

Table 6-2. Analytical Methods for Determining Diazinon and Transformation Products in Environmental Samples (continued)

Sample matrix ^a	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water, river water	Preconcentration of 2.5 mL water onto C ₁₈ extraction disks, rinsing with additional 1 mL and purging disk with gas to remove residual water. Elution with ethyl acetate directly onto GC pre-column with solvent venting.	GC/NPD	Tap water: 20 pg/mL (ppt); river water: 20–50 pg/mL	>95 (<4% RSD at 200 ppt)	Kwakman et al. 1992
Pond water	Micro liquid-liquid extraction of 1.5 mL water with 1.5 mL methyl t-butyl ether. 500 µL of extract slowly introduced into GC pre-column with solvent venting.	cap. GC/FPD	0.02 µg/L (ppb)	102 (5% RSD) at 0.50 µg/l level	van der Hoff et al. 1993
Surface water	Adsorption of pesticides from 2 L of water onto XAD-2 and XAD-7 resins. Elution with methylene chloride, water removal and use of K-D to reduce volume.	GC/chemical ionization ion trap MS	0.0005 ppb (0.5 ppt)	103.8 (14% CV) at 1 ppb level	Mattern et al. 1991
Water	1. Liquid/liquid extraction (EPA Method 3510); 2. continuous liquid/liquid extraction (EPA Method 3520).	GC/FPD (EPA Method 8140)	6 µg/L (ppb)	No data	EPA 1986a, 1986c, 1986d
Water	Filtration of 1 L of water followed by extraction 3 times with 100 mL methylene chloride after addition of 20 g sodium sulfate. Concentration using K-D and solvent exchange to benzene. Concentrations done under nitrogen. Fractionation by HPLC.	GC/FPD (P-mode)	0.025 µg/kg (ppb or 25 ng/kg, ppt)	92 (2% RSD)	Seiber et al. 1990

Table 6-2. Analytical Methods for Determining Diazinon and Transformation Products in Environmental Samples (continued)

Sample matrix ^a	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Solid-phase microextraction (SPME) of filtered water sample; thermal desorption of diazinon from SPME fiber.	GC/AED	1 µg/L (ppb) with carbon line (193 nm); 3 µg/L with S line (181 nm).	No data (precision 8–12 relative standard deviation)	Eisert et al. 1994
Water	Extraction of analytes from water using SPE; elution with ethyl acetate (108 µL) directly onto retention gap with solvent venting.	GC/AED	1 ng/L (100 mL sample) with P channel.	105 (4% RSD) at 5 µg/L.	Hankemeier et al. 1995
Industrial and municipal waste water	Extraction of 1 L of sample with 60 mL methylene chloride 3 times. Water removal from extract and solvent exchange to hexane during K-D concentration.	GC/FPD or thermionic detection (P-mode); GC/MS for qualitative identifications recommended. (Method 1657)	0.6 µg/L (ppb)	67 (6% (RSD)	EPA 1992a
Waste water	Extraction of 1 L of water with 15% methylene chloride in hexane using a separatory funnel. Concentration using K-D. Clean up (if needed) by Florisil fractionation or acetonitrile partition.	GC/FPD (P-mode) or GC/thermionic detection. GC/MS for qualitative compound identification recommended. (Method 614)	0.012 µg/L (ppb); (12 ng/L, ppt)	94 (5.2% RSD)	EPA 1992b

Table 6-2. Analytical Methods for Determining Diazinon and Transformation Products in Environmental Samples (continued)

Sample matrix ^a	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Direct injection or liquid/liquid extraction and concentration.	HPLC/UV	0.5 mg/L (ppm, direct injection); 0.5 µg/L (ppb, liquid/liquid extraction)	No data	Mallet et al. 1990
Soil (diazinon, diazoxon, 2-isopropyl-4-methyl-6-hydroxy-pyrimidine)	Extraction of soil with hexane:acetone (1:1), centrifugation, separation of hexane from acetone/water layer. Extraction of acetone/water phase with chloroform:diethyl ether (1:1), solvent exchanged to methanol. Hexane layer contained diazinon, chloroform/diethyl ether fraction contained 2-isopropyl-4-methyl-6-hydroxy-pyrimidine.	TLC	No data	No data	Sethunathan and Yoshida 1969
Soil (diazinon, 2-isopropyl-4-methyl-6-hydroxy-pyrimidine)	Sequential Soxhlet using acetone then methanol.	GC, TLC, GC/MS	No data	No data	Burkhard and Guth 1979

Table 6-2. Analytical Methods for Determining Diazinon and Transformation Products in Environmental Samples (continued)

Sample matrix ^a	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water, soil	<p><u>Water</u>: Addition of deuterated standards to 1 L water and extraction 3 times with 200 mL methylene chloride. Water removal with anhydrous sodium sulfate then concentration using K-D and nitrogen blowdown.</p> <p><u>Soil</u>: Addition of 10 mL water and deuterated standards to 50 g of soil followed by equilibration for 1 h. Sonication 3 times with acetone/hexane. Phase separation followed by water removal using sodium sulfate, concentration using K-D, and nitrogen blow-down. Spiking with phenanthrene-d₁₀ before analysis.</p>	GC/MS(SIM)	100–200 ppt for water, 2–4 ppb for soil	<p>Water: 89.4 (4.4% RSD) at 1 ppb</p> <p>Soil: 103 (15% RSD) at 20 ppb</p>	Lopez-Avila et al. 1985
Waters, soils, sediments, sludges	<p><30% solids: Dilution to 1% solids and extraction with methylene chloride, concentration using K-D. Clean up using GPC and SPE.</p> <p>>30% solids: Sonication with acetonitrile and methylene chloride; back extraction with water, concentration using K-D; clean up using GPC and SPE.</p>	GC/FPD (Method 622)	3.8 ng/L	60–120	EPA 1992c

Table 6-2. Analytical Methods for Determining Diazinon and Transformation Products in Environmental Samples (continued)

Sample matrix ^a	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soils, sludges, and solid waste	1. Soxhlet extraction (EPA Method 3540). 2. Sonication (EPA Method 3550). Cleanup using Florisil (EPA Method 3620) or GPC (EPA Method 3640).	GC/FPD (EPA Method 8140)	Low-level soil by sonication/ GPC cleanup: 400 µg/L; High-level soils and sludges by sonication: 6 mg/L; Non-water miscible waste: 60 mg/L	No data (depends on matrix)	EPA 1986a, 1986e, 1986f, 1986h, 1986i
Cucumber, lettuce, grapes	Chopping of produce and extraction with acetone/methylene chloride/petroleum ether (1:1:1). Evaporation to dryness and redissolution in acetone and concentration.	SFC/NPD	No data	No data	Zegers et al. 1994a
Green beans, lettuce, carrot, bell pepper	Homogenization of produce with acetonitrile. Addition of NaCl to affect phase separation, removal of acetonitrile, water removal volume reduction, addition of deuterated internal standards.	GC/MS	50 ppb	88 (17% RSD)	Liao et al. 1991
Kale, endive, carrots, lettuce, apples, potatoes, strawberries	Extraction of crops with ethyl acetate and granular sodium sulfate, filtration, concentration with K-D. Sweep co-distillation cleanup for GC. Florisil partition chromatography for polarographic confirmation.	GC/KCl thermionic detector or GC/FPD; polarographic confirmatory method	No data for GC; polarographic: 0.2 ppm based on 1 g crop in 1 mL cell	No data	AOAC 1990

Table 6-2. Analytical Methods for Determining Diazinon and Transformation Products in Environmental Samples (continued)

Sample matrix ^a	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Numerous non-fatty crops	Extraction with acetonitrile and partition into petroleum ether. Concentration using K-D and purification using Florisil column chromatography.	GC/KCl thermionic detector; identifications by combinations of gas, thin layer, and paper chromatography	No data	≥80	AOAC 1990
Soybeans and rice	Grinding of 25 g samples and extraction with 150 mL of 2:1 acetone: methanol; filtration and reduction of volume to 100 mL. Addition of water, NaCl followed by extraction with methylene chloride (2x); solvent evaporation and redissolution in methylene chloride:cyclohexane (1:1) and fractionation on Bio-Bead S-X3. Evaporation under N ₂ stream and redissolution in 2 mL hexane.	GC/NPD or GC/MS (SIM)	Rice: 0.01 ppm soybeans: 0.05 ppm	Rice: 83.4 (1.5% RSD) at 1 ppm soybeans: 62.7 (8.6% RSD) at 1 ppm	Hong et al. 1993
Various fruits and vegetables	Homogenization of sample (adding water if needed) and adsorption on activated Florisil to produce a free-flowing powder. Elution with ethyl acetate or methylene chloride.	GC/NPD	4 µg/kg (ppb)	91–103 at 0.05 mg/kg	Kadenczki et al. 1992
Various produce	Homogenization of sample and extraction with acetonitrile, filtration, addition of salt and solvent evaporation. Redissolution of residue in acetone for analysis.	GC/FPD or alkali FID	100 ppb	96 (17% RSD)	Hsu et al. 1991

Table 6-2. Analytical Methods for Determining Diazinon and Transformation Products in Environmental Samples (continued)

Sample matrix ^a	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Various prepared foods	Blending of sample with acetone, filtration and transfer to Hydromatrix column. Elution with methylene chloride and concentration.	GC/FPD	No data	91 at 100 ppb	Hopper 1988
Pasta, eggs	Blending of samples with acetone and extraction with dichloromethane and acetone, water removal and volume reduction. Cleanup using carbon-celite (pasta) or C ₁₈ SPE (eggs).	GC/FPD	approx. 1 ppb	Pasta: 80 at 30 ppb; eggs: 93 at 13 ppb	Leoni et al. 1992
Milk	Extraction of milk 3 times with 70% acetonitrile in water, filtration, removal of fat by zinc acetate addition, and partitioning with methylene chloride. Reduction of volume after drying.	GC/FPD (P-mode)	10 ppb	89 (3.8% RSD) at 100 ppb	Toyoda et al. 1990
Lanolin	Dissolution in hexane and extraction with acetonitrile. Addition of 5% NaCl in water to acetonitrile and back-extraction with hexane. Washing of hexane extract with water, volume reduction and fractionation using Florisil.	GC/FPD (526 nm); GC/atomic emission detection; GC/MS	GC/FPD 0.03 ppm; GC/AED 0.6 ppm(P); 0.3 ppm(S); GC/MS 0.6 ppm	90 (6.4% RSD) at 1 ppm 95 (5.6% RSD) at 2 ppm	Miyahara et al. 1992

^a Unless otherwise stated, diazinon was determined

FPD = flame photometric detector; GC = gas chromatography; GPC = gel permeation chromatography; HPLC = high performance liquid chromatography; K-D = Kùderna-Danish; MS = mass spectrometry; NPD = nitrogen phosphorus detector; SFC = supercritical fluid chromatography; SIM = selected ion monitoring; SPE = solid phase extraction; UV = ultraviolet absorbance detection

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animal samples and should be applicable to human samples, but such an application would need to be validated.

Kirkbride (1987) described the estimation of diazinon in human omental tissue (fatty tissue) after a fatal poisoning. In this method, the tissue was pulverized and extracted with acetone. After extract concentration and purification by sweep co-distillation and Florisil fractionation, diazinon was measured by gas chromatography (GC) with nitrogen-phosphorus detection (NPD). After another fatal diazinon poisoning, diazinon was quantified by GC/electron capture detection (ECD) and GC/flame ionization detection (FID) by Poklis et al. (1980). The diazinon in human adipose, bile, blood, brain, stomach contents, kidney, and liver was recovered by macerating the sample with acetonitrile followed by the addition of aqueous sodium sulfate and extraction into hexane. Following an adsorption chromatography clean-up, the sample was analyzed.

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

Diazinon was determined in bovine liver and rumen content by GC/flame photometric detection (FPD) by Holstege et al. (1991) using a method with a limit of detection (LOD) reported to be 0.01-0.05 $\mu\text{g/g}$ using a 5 g sample. Recoveries were reported to be 95% from rumen content and 88% from liver. In another study, diazinon was determined by GC/FPD and GC/mass spectrometry (MS) in avian liver and kidney using a method with a LOD of 0.02 ppm and 100% recovery at the 0.05 ppm level. Brown et al. (1987) used GUFPD to determine diazinon in animal fat. No data were reported for the LOD, but the recovery was stated to be 90% (6% RSD) at 0.4 ppm.

Animal fat was studied using sweep codistillation (Brown et al. 1987). Good recovery (90%) was measured at 0.4 mg/kg; no LOD information was given. Diazinon in liver and rumen content was determined by GC/FPD after methanoVdichloromethane (1:9) extraction and clean-up using either gel permeation chromatography (GPC) or silica gel solid phase extraction (SPE). The LODs were

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reported to range from 10 to 50 $\mu\text{g/g}$ using a 5 g sample with measured recoveries of diazinon from rumen content of 95% at 0.1 $\mu\text{g/g}$ and from liver of 88% at 0.05 $\mu\text{g/g}$.

The mode of injection in GC-based methods can affect the recoveries of diazinon. In a study of the determination of organophosphorus pesticides in milk and butterfat, it was found that the recoveries of diazinon from butterfat, calculated relative to organic solutions of standard compounds, were 125% and 84% for splitless and hot on-column injections, respectively (Erney et al. 1993). Recoveries from milk were not dependent on the mode of injection. It was concluded that the sample matrix served to increase diazinon transfer to the GC column by reducing thermal stress imposed on the analytes and by blocking active sites within the injector. Therefore, on-column injection should be used in order to prevent bias when organic solutions of standard compounds are used for quantitation; if this is not possible, the matrix must be present at low concentrations or the calibration standards must be prepared in residue-free samples to avoid unknown bias.

6.2 ENVIRONMENTAL SAMPLES

Diazinon residues are found throughout the environment in air, water, soil, sediments, sludges, and other solid wastes because of the use of this compound for agricultural purposes. The use of diazinon on crops presents the possibility of residues in products for human consumption, making food an important potential route of exposure for this compound.

Diazinon can be measured in air after pre-concentration from air onto some adsorbent material with subsequent extraction. Following extraction from the adsorbent, separation and detection methods include GUMS (Hsu et al. 1988; Kuwata and Yasuhara 1994) GC/NPD (Williams et al. 1987), and GC/FPD in the P mode (NIOSH 1994). The method of Williams et al. (1987) applicable to both diazinon and diazoxon. The NIOSH method (Method 5600, NIOSH 1994) has been fully validated for use in occupational settings where regulatory exposure limits are of concern.

Many methods for the determination of diazinon in environmental media have been published by the EPA (see Table 6-2). For surface water and industrial and municipal waste waters, Methods 622, 614, and 1657 and preparation Methods 3510/3520 in conjunction with analytical Method 8140 (EPA 1986a, 1986b, 1986c, 1992a, 1992b, 1992c) can be used. All of the methods employ some form of liquid/liquid extraction, extract volume reduction, and GC in conjunction with selective detection

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(e.g., FPD, thermionic detection, or MS). Reported LODs range from a high of approximately 6 µg/L (SW846 Method 8140 applied to water) down to 12 ng/L (Method 614) (EPA 1986a, 1992b). In most cases, the recovery will be dependent upon the particular matrix. For Method 1657, recoveries in the range of 60-120% are considered acceptable. Average recoveries were reported to be 67% for Method 622 and 94% for Method 614 (EPA 1992a, 1992b, 1992~). Methods are also available for soils, sludges, sediments, and solid wastes. Sample preparation typically involves liquid/liquid extraction in a separatory funnel, in a Soxhlet extractor, or with sonication. The more complex samples (some waters and most soils, sediments, sludges, or solid wastes) need to be subjected to some clean-up method before analysis. The use of Florisil, GPC, and SPE are common approaches. Diazinon is determined by GC/FPD (EPA 1986a, 1992c).

Although not specific for diazinon, some general interferences were noted in the EPA methods. Careful attention must be paid to the cleanliness of the reagents and glassware (EPA 1986b, 19868). Trace impurities can become major impurities during extract concentration steps. In addition, soap residues on glassware can cause the degradation of organophosphorus pesticides (EPA 1986b).

Many other methods were reported for the determination of diazinon in water. Sample preparation methods include either some form of liquid/liquid extraction or the use of SPE, usually C₁₈-silica, for isolation of diazinon residues. Mallet et al. (1990) reported a method for environmental water based on high performance liquid chromatography/ultra violet (HPLCKJV) absorbance detection with either direct injection of the water or of an aliquot of an extract. The LODs were as low as 0.5 µg/L with the extraction approach. Mattern et al. (1991) reported a LOD for diazinon in surface water of 0.0005 ppb using GC in conjunction with chemical ionization ion trap MS. Lopez-Avila et al. (1985) reported an isotope dilution GC/MS selected ion monitoring (SIM) method that is applicable to water or soil after solvent extraction. Recoveries were stated to be 89% at 1 ppb in water and 103% at 20 ppb in soil. An LOD of 0.025 µg/kg was reported for diazinon in water with a recovery of 92% (2% RSD) by Seiber et al. (1990). SPE provides an easy method to isolate residues and can greatly reduce the amounts of solvent used in sample preparation. Driss et al. (1993) preconcentrated diazinon from drinking water onto C₁₈-silica or polystyrene-divinylbenzene co-polymer with a subsequent backflush onto an HPLC column (UV detection). LODs as low as 30 µg/L were reported. Kwakman et al. (1992) preconcentrated diazinon from drinking and river water onto C₁₈-SPE disks and eluted the adsorbed compounds directly into a GC pre-column. The solvent was vented away from the analytical column during the elution step. Detection was by NPD and excellent LODs (20 pg/L) and

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recoveries (greater than 95% with less than 4% RSD at 200 pg/L) were reported. Although most of the SPE methods boasted good recoveries and LODs, one reference noted that the pesticide can associate with dissolved organic matter (primarily humic materials) resulting in poor retention by the SPE material (Johnson et al. 1991). This can reduce method recoveries.

Diazinon has a finite vapor pressure (see Chapter 3) and thus will be present in the air. A method for diazinon in air has been reported that is based on the use of polyurethane foam (PUF) to adsorb the pesticide from the air as the air is pulled through the PUF (Hsu et al. 1988). The PUF is then Soxhlet-extracted and the extract volume reduced prior to capillary GC/MS analysis. An LOD of 55 ng/m³ (5.5 m³ sample) and recovery of 73% were reported. Another study was described in which the diazinon levels in indoor air were monitored following periodic application of the pesticide for insect control (Williams et al. 1987). In this method, air is pulled through a commercially available adsorbent tube to concentrate diazinon. The tube is then extracted with acetone prior to GC/NPD analysis. No data were provided for the LOD, but recoveries in excess of 90% were reported at the 0.1 and 1 µg/m³ levels. This paper also indicated that diazinon can be converted to diazoxon by ozone and NO_x in the air during the sampling process.

SFE also would appear to have utility in sample preparation methods. Lopez-Avila et al. (1992) applied SFE to the recovery of a variety of analytes, including organophosphorus pesticides, from solid matrices. The unoptimized extraction from sand gave a recovery of 54% for diazinon. Supercritical trifluoromethane has been shown to extract diazinon from glass beads with a recovery of 86% (Hillmann and Bachmann 1995). Organophosphorus pesticides have also been recovered from Tenax-GC, an adsorbent used to collect diazinon during air sampling, and analyzed directly by GC (Raymer and Velez 1991). More SFE-based methods will likely appear in the future. Supercritical fluid chromatography (SFC) has also been used for the determination of diazinon in water where 75 µL were injected (Zegers et al. 1994b). Using thermionic detection, the LOD was about 1 µg/L (1 ppb) with a reproducibility of better than 7% at the 5-15 µg/L level. The same authors also published an SFC-based method for cucumber, lettuce, and grapes (Zegers et al. 1994a) but did not specify the LOD and recovery.

The determination of diazinon in foods is important because this chemical is used as a pesticide on plant crops and, at least in some cases, in pesticide dips for the control of parasitic infestations in animals (Brown et al. 1987; Miyahara et al. 1992). Because animals are exposed to this compound,

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both via pesticide dips and by ingestion of crops to which diazinon has been applied, some methods have been reported for animal products. The majority of methods, however, deal with the determination of residues in plant products. Most of the analytical methods found that describe the extraction from, and determination of, diazinon residues in various crops (plant materials) were developed as part of multiresidue methods. They are based on homogenization of the sample with an organic solvent (polar or non-polar); the isolation of the residues from this initial extract; and, usually, some additional cleanup prior to the analysis of the extract by GC. The most common non-MS modes of detection exploit the presence of phosphorus or sulfur (FPD) or phosphorus or nitrogen-thermionic, NPD. Whenever possible, the MS mode of detection also provides confirmation of the structure thus increasing the certainty of the identification. The acquisition of full-scan data is the most convincing for confirmatory analyses, although the method LOD tends to be adversely affected. The use of SIM MS can improve the LOD over full-scan analysis and can often provide sufficient selectivity, if the appropriate number of specific ions are chosen, for high confidence in the chemical identity. It is also common to see the analysis of a particular extract on two GC columns coated with phases of different selectivity. The coelution of a peak in the sample with the peak associated with a chemical standard on both stationary phases greatly increases the probability that the unknown is indeed the same chemical as the standard.

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

Several methods employ the homogenization of the plant material with aqueous acetonitrile (Hsu et al. 1991; Liao et al. 1991) or other polar organic solvents such as acetone/methanol mixtures (Hong et al. 1993). Phase separation is brought about with the addition of a salt. The acetonitrile approach is preferred by the California Department of Food and Agriculture because of the higher recoveries

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possible (see Table 6-2) (Lee et al. 1991). The advantage of acetonitrile is found in its ability to more readily solvate residues and in the ease with which the phase separation can be accomplished through the addition of salt (Lee et al. 1991). Reported LODs for diazinon were typically 10-50 ppb. One of the methods eliminated any clean-up steps after the initial extraction (Hsu et al. 1991) to provide a method with a faster turnaround time with some loss in sensitivity (LOD approximately 100 ppb) relative to the purified samples.

The method published by Kadenczki et al. (1992) combined sample extraction with extract cleanup by adsorbing a homogenized sample (various fruits and vegetables) onto the surface of activated Florisil to obtain a free-flowing powder. This was packed into a column and the organophosphate residues were eluted with ethyl acetate or methylene chloride. Good recoveries (91-103%) were obtained at the 0.05 mg/kg (50 ppb) level, with an LOD estimated to be 4 µg/kg (4 ppb) when using GUNPD.

Methods found for the determination of diazinon in animal products also used homogenization with a polar organic solvent as the first step in residue recovery. Toyoda et al. (1990) isolated diazinon from milk via partition into methylene chloride after extraction of the milk with 70% acetonitrile in water. Based on GC/FPD, an LOD of 10 ppb and a recovery of 89% (3.8% relative standard deviation) at 100 ppb were reported. Diazinon residues in eggs were studied (Leoni et al. 1992) after blending the eggs with acetone and partitioning into dichloromethane and acetone followed by C₁₈-silica SPE. Based on GC/FPD analysis, an LOD of 1 ppb and a recovery of 93% at 13 ppb were reported.

Some alternate GC detection schemes that can provide unique selectivity in the determination of organophosphorus pesticides were reported. Although they require more expensive hardware, such approaches might prove useful in selected applications or if the hardware is currently available in the laboratory. Stan and Kelner (1989) have described a method for the GUMS confirmation of organophosphorus pesticides using pulsed positive-negative ion chemical ionization (PPNICI). This method generates base peaks with high masses in the positive ion mode and group-specific fragments of high intensity-in the negative ion mode. Ions to be monitored are recommended for 72 compounds, including diazinon.

With GC in conjunction with atomic emission detection (AED) and the simultaneous monitoring of emission wavelengths from a microwave plasma for several heteroatoms (e.g., S, P, Cl, N), selectivity in the analysis of complex samples can be greatly increased (Wylie and Oguchi 1990). GUAED was

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claimed to provide greater selectivity than the more common GC detectors (FPD, NPD) used for the analysis of organophosphorus compounds (Lee and Wylie 1991). Methods for diazinon in water using GUAED have been published (Eisert et al. 1994; Hankemeir et al. 1995). The products formed in the plasma can also be introduced into a mass spectrometer to increase selectivity and provide additional information about the atomic composition (Story and Caruso 1993). Both AED and NICI should be applicable to both biological and environmental samples.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of diazinon is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of diazinon.

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

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Section 2.6.1 reported on biomarkers used to identify or quantify exposure to diazinon. Some methods for the detection of the parent compound in biological samples were described above. The parent chemical is quickly metabolized so the determination of metabolites can also serve as biomarkers of exposure. The most specific biomarkers will be those metabolites related to 2-isopropyl-6-methyl-4-hydroxypyrimidine. A method for this compound and 2-(1'-hydroxy-1'-methyl)-ethyl-6-methyl-4-hydroxypyrimidine in dog urine has been described by Lawrence and Iverson (1975) with reported sensitivities in the sub-ppm range. Other metabolites most commonly detected are 0,0-diethylphosphate and 0,0-diethylphosphorothioate, although these compounds are not specific for diazinon as they also arise from other

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diethylphosphates and phosphorothioates (Drevenkar et al. 1993; Kudzin et al. 1991; Mount 1984; Reid and Watts 1981; Vasilic et al. 1993). Another less specific marker of exposure is erythrocyte acetyl cholinesterase, an enzyme inhibited by insecticidal organophosphorus compounds (see Chapter 2). Methods for the diazinon-specific hydroxypyrimidines should be updated and validated for human samples. Rapid, simple, and specific methods should be sought to make assays readily available to the clinician. Studies that relate the exposure concentration of diazinon to the concentrations of these specific biomarkers in blood or urine would provide a basis for the interpretation of such biomarker data.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Human exposure to diazinon occurs via inhalation of ambient air; ingestion of contaminated food and water; and dermal uptake through occupational and nonoccupational contact with contaminated soils, surface water, and commercial preparations. Methods have been reported for the measurement of diazinon in various foods, soils, sludges, sediment, solid wastes, waste water, drinking water, and air. The MRLs established for diazinon are 0.009 mg/m³ (90 µg/m³; 3.7 ppb) for intermediate-duration inhalation and 0.0002 mg/kg/day for intermediate duration oral exposure. The methods of Hsu et al. (1988) (LOD of 55 µg/m³) and Kawata and Yasuhara (1994) (LOD of 0.5 µg/m³) are adequate for the determination of diazinon in air. If a 70-kg individual is assumed, method LODs of 0.007 mg/L (7 ppb) and 0.007 mg/kg (7 ppb) in water and foods, respectively, are required for the method to be adequate at the oral intermediate MRL. All of the methods for detection of diazinon in water shown in Table 6-2 are adequate. With regard to foods, the methods of Kadenczki et al. (1991) and Leoni et al. (1992) for detection of diazinon are adequate. Methods for other non-fatty crops would need to be validated or developed if routine use were desired. Additional methods for detection of diazinon in fatty foods are needed to permit the evaluation of the residues in those fatty media.

There are also methods for the analysis of diazinon degradation products in air, water, and soil. Williams et al. (1987) published a method for diazinon and its oxon (diazoxon) in air. Other methods have been reported for diazinon, its oxon, and hydrolysis products in water (Suffet et al. 1967), soils and water (Lichenstein et al. 1968), and soil (Burkhard and Guth 1979). The hydrolysis product 2-isopropyl-6-methyl-4-hydroxypyrimidine was studied along with diazoxon in submerged soil (Sethunathan and Yoshida 1969). Suffet et al. (1967) demonstrated the ability of GC to separate diazinon, diazoxon, and 2-isopropyl-6-methyl-4-hydroxypyrimidine. However, no validated methods

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for the determination of diazoxon or 2-isopropyl-6-methyl-4-hydroxypyrimidine were found. Thus, additional methods are needed for the quantitative analysis of diazinon transformation products in environmental matrices. It will also be important to establish MRLs for the transformation products to put the analytical requirements into perspective.

6.3.2 Ongoing Studies

The following ongoing studies on analytical methods for diazinon were found.

- 1) The University of Maryland, Eastern Shore, Human Ecology, is evaluating the ability of various fabrics to reduce exposure to diazinon and is evaluating the effectiveness of decontamination procedures.
- 2) The Department of Food Science at the University of Maine, Orono, is developing methods for diazinon in food, water, and soils based on GC/AED, HPLC, and immunoassays.
- 3) The University of Nevada, Range Wildlife and Forestry, Reno, is developing and evaluating methods for determining diazinon and conversion products in air and atmospheric moisture.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding diazinon in air, water, and other media are summarized in Table 7- 1.

ATSDR has derived an intermediate-duration inhalation MRL of 0.009 mg/m³ for diazinon based on brain acetylcholinesterase inhibition in rats Hartman (1990).

ATSDR has derived an intermediate-duration oral MRL of 0.0002 mg/kg/day for diazinon based on brain acetylcholinesterase inhibition in offspring of mice maternally exposed to diazinon during gestation (Barnes 1988).

The reference dose for diazinon is undergoing review by an EPA Workgroup. No reference concentration exists for the compound.

Diazinon has no cancer classification under the International Agency for Research on Cancer (IARC), the U.S. Environmental Protection Agency, or the National Toxicology Program (NTP).

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), food tolerance restrictions for diazinon range from 0.1 to 60 ppm (EPA 1982).

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Table 7-1. Regulations and Guidelines Applicable to Diazinon

Agency	Description	Information	Reference
<u>INTERNATIONAL</u>			
WHO		NA	
IARC	Group (cancer ranking)	NA	
<u>NATIONAL</u>			
Regulations:			
a. Water:			
EPA/OW	Designation of Hazardous Substances	Yes	40 CFR 116.4 EPA 1978a
	Reportable Quantities of Hazardous Substances: Section 311 of Clean Water Act	1 lb.	40 CFR 117.3 EPA 1979a
	Appendix D - NPDES Permit Application Testing Requirements (122.21)	Yes	40 CFR 122 EPA 1983
	Form 2D	Yes	40 CFR 122 EPA 1983
	Instructions - Form 2c	NA	40 CFR 125 EPA 1979b
	Identification of Test Procedures	Yes	40 CFR 136.3 EPA 1973
b. Food:			
EPA/OPTS	Tolerance Range for Agriculture Products	0.1 - 60 ppm	40 CFR 180.153 EPA 1971
e. Other:			
EPA/OERR	Reportable Quantity	1 lb.	40 CFR 302.4 EPA 1985a
EPA/OPTS	Food Additives Permitted in Food for Human Consumption: Diazinon in Food Handling Establishments - Application Specs.	Yes	40 CFR 185.1750 EPA 1982
	Feed Additives Permitted in Animal Feed: Diazinon in Feed Handling Establishments - Application Specs.	Yes	40 CFR 186.1750 EPA 1982

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Diazinon (Continued)

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
	Applicability; Description of the Organic Pesticide Chemicals Manufacturing Subcategory	Yes	40 CFR 455.20 EPA 1978b
Guidelines:			
a. Air:			
ACGIH	Ceiling limit for Occupational Exposure (TLV-TWA)	0.1 mg/m ³ (8.0x10 ⁻³ ppm) (skin)	ACGIH 1996
NIOSH	Recommended Exposure Limit for Occupational Exposure (TWA)	0.1 mg/m ³ (8.0x10 ⁻³ ppm) (skin)	NIOSH 1992
b. Water:			
EPA	1-d Health Advisory (child & adult)	0.02 mg/L (child)	EPA 1995
	10-d Health Advisory (child & adult)	0.02 mg/L (child)	EPA 1995
	Lifetime Health Advisory (child & adult)	0.0006 mg/L (adult)	EPA 1995
	Longer-term Health Advisory (child & adult)	0.005 mg/L (child) 0.02 mg/L (adult)	EPA 1995 EPA 1995
c. Other:			
EPA	Cancer classification	NA	
NTP	Cancer classification	NA	
<u>STATE</u>			
Regulations and Guidelines			
a. Air:			
	Acceptable Ambient Air Concentration Guidelines or Standards		NATICH 1992
AZ	1 hr avg. time	2.40 µg/m ³ (1.98x10 ⁻⁴ ppm)	
	24 hr avg. time	8.00 µg/m ³ (6.43x10 ⁻⁵ ppm)	

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Diazinon (Continued)

Agency	Description	Information	Reference
<u>STATE</u> (Cont.)			
CT	8 hr avg. time	2.00 $\mu\text{g}/\text{m}^3$ (1.61×10^{-7} ppm)	
FL-PINELLA	8 hr avg. time	1.00 $\mu\text{g}/\text{m}^3$ (8.03×10^{-5} ppm)	
	24 hr avg. time	2.40×10^{-1} $\mu\text{g}/\text{m}^3$ (1.93×10^{-5} ppm)	
ND	8 hr avg. time	1.00×10^{-3} mg/m^3 (8.03×10^{-8} ppm)	
NV	8 hr avg. time	2.00×10^{-3} mg/m^3 (1.61×10^{-7} ppm)	
TX	30 min avg. time	1.00 $\mu\text{g}/\text{m}^3$ (8.03×10^{-5} ppm)	
	Annual avg. time	1.00×10^{-1} $\mu\text{g}/\text{m}^3$ (8.03×10^{-6} ppm)	
VA	24 hr avg. time	1.70 $\mu\text{g}/\text{m}^3$ (1.37×10^{-4} ppm)	
WA-SWEST	24 hr avg. time	3.00×10^{-1} $\mu\text{g}/\text{m}^3$ (2.41×10^{-5} ppm)	
b. Water:			
Water Quality: Human Health			
AZ	Drinking water guideline	0.63 $\mu\text{g}/\text{L}$	FSTRAC 1990
CA	Drinking water guideline	14 $\mu\text{g}/\text{L}$	
FL	Domestic/Drinking water	10 $\mu\text{g}/\text{L}$	Sittig 1994
KS	Drinking water guideline	0.63 $\mu\text{g}/\text{L}$	FSTRAC 1990
ME	Drinking water guideline	0.63 $\mu\text{g}/\text{L}$	
MI	Domestic/Drinking water	0.63 $\mu\text{g}/\text{L}$	Sittig 1994
MN	Drinking water guideline	0.6 $\mu\text{g}/\text{L}$	FSTRAC 1990
NY	Domestic/Drinking water	0.7 $\mu\text{g}/\text{L}$	Sittig 1994

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Table 7-1. Regulations and Guidelines Applicable to Diazinon (Continued)

Agency	Description	Information	Reference
RI	Drinking water guideline	0.6 µg/L	FSTRAC 1990
VT	Drinking water standard	0.63 µg/L	
STATE (Cont.)			
OH	Water Quality: Aquatic Life		CELDS 1993
	Exceptional, modified, & seasonal warmwater; outside mixing zone; 30-d avg.	0.009 µg/L	
	Coldwater & limited resource warmwater; outside mixing zone; 30-d avg.	0.009 µg/L	
NY	Groundwater Quality Standards	0.7 µg/L (Class GA)	CELDS 1993

NOTE: Update of drinking water guidelines and other areas in progress.

Units in table reflect values and units of measure designated by each agency in its regulations or advisories.

ACGIH = American Conference of Governmental and Industrial Hygienists; CELDs = Computer-aided Environmental Legislative Database; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; FSTRAC = Federal State Toxicology and Regulatory Alliance Committee; IARC = International Agency for Research on Cancer; LDR = Land Disposal Restriction; NA = Not available at the present time; NATICH = National Air Toxics Information Clearinghouse; NIOSH = National Institute of Occupational Safety and Health; NPDES = National Pollution Discharge Elimination System; NTP = National Toxicology Program; OERR = Office of Emergency and Remedial Response; OPTS = Office of Pesticides and Toxic Substances; OSHA = Occupational Safety and Health Administration; OW = Office of Water; TLV = Threshold Limit Value; TW A = Time Weighted Average; WHO = World Health Organization

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9. GLOSSARY

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

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

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

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

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

Carcinogen -- A chemical capable of inducing cancer.

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

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

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

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

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

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

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

9. GLOSSARY

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

In vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In vivo -- Occurring within the living organism.

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

Lethal Concentration₍₅₀₎ (LC₅₀) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose_(LO) (LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

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

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

Minimal Risk Level -- An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

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

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

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

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

9. GLOSSARY

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

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

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

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

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

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

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

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

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

Toxic Dose (TD₅₀) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

ATSDR MINIMAL RISK LEVEL

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

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

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

APPENDIX A

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

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Diazinon
CAS number: 333-41-5
Date: August 1996
Profile status: Final
Route: [X] Inhalation [] Oral
Duration: [] Acute [X] Intermediate [] Chronic
Key to figure: 5
Species: Rat

MRL: 0.009 [] mg/kg/day [] ppm [x] mg/m³
Reference: Hartman HR (1990) 21 -day repeated exposure inhalation toxicity in the rat.
Project

No. 891205. An unpublished report dated June 8, 1990 from Ciba-Geigy Basel/Switzerland.
EPA-41557402.

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details): This is a 21-day repeated exposure inhalation toxicity to diazinon using a nose-only exposure system. Four groups of albino rats (10 males [15 l-200 g] and 10 females [142-179 g] each) were exposed to various concentrations of aerosol diazinon (0,0.05,0.46, 1.57, and 11.6 mg/m³) diluted in ethanol for 6 hours a day, 5 days a week for 3 weeks. Particle size analysis was done to ensure that the test aerosols were in the respirable range for the rat. Two control groups were used, one exposed to humidified filtered air only and the other to the carrier vehicle ethanol (21.54 g/m³). The test substance was the liquid MG-8 formulation (88% diazinon). Exposure levels were monitored by gas chromatography. Clinical examinations included ophthalmology, body weight, food consumption, hematology, and blood chemistry (including serum cholinesterase and erythrocyte acetylcholinesterase). The termination of the exposure period was followed by gross necropsy, brain acetylcholinesterase, organ weight determination, and histopathology of the nasal tissues and lungs from all groups and the spleen, heart, liver, kidney, adrenal gland, and any tissue with gross lesions from the control and 11.6 mg/m³ groups.

Effects noted in study and corresponding doses:

No deaths or changes in body weights or food consumption were observed. Piloerection was observed in most animals, particularly during the first week into the exposure, with the incidence gradually declining during weeks 2 and 3 of exposure. This sign was neither exposure nor dose-related and no clinical signs of organophosphate toxicity were observed. No exposure-related ophthalmoscopic or histopathological lesions were found (nasal tissues and lungs, spleen, heart, liver, kidney, and adrenal gland). Minimally lower values of red blood cell parameters (erythrocyte count, hemoglobin, and packed red cell volume) were observed in the highest dose (11.6 mg/m³) females but were not statistically significant. A statistically significant higher lung to body weight ratio was observed in the females only at exposures of 0.46 and 1.57 mg/m³ but not at 11.6 mg/m³. Since no histopathological evidence of adverse effects to the lung was reported, the toxicological significance of this finding is uncertain. Statistically significant reductions at study termination in serum cholinesterase (marker for exposure) were seen in males at 1.57 mg/m³ (14%) and 11.6 mg/m³ (19%) and in females at 0.46 mg/m³ (20%), 1.57 mg/m³ (27%), and 11.6 mg/m³ (43%). Statistically significant reductions in erythrocyte acetylcholinesterase (surrogate marker for neural acetylcholinesterase) were seen in males at 11.6 mg/m³ (36%) and in females at 1.57 mg/m³ (10%) and 11.6 mg/m³ (39%). Statistically significant reductions in brain acetyl-

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cholinesterase were not seen in males, but were seen in females at 0.05 mg/m³ (24%), 0.46 mg/m³ (17%), 1.57 mg/m³ (20%), and 11.6 mg/m³ (37%).

Effect of Aerosol Diazinon on Cholinesterase Activities

	Serum ChE	Erythrocyte AChE	Brain AChE
<u>Males</u> (week 4)			
0.05 mg/m ³	+9%**	+2%	-1%
0.46 mg/m ³	-5%	-5%	+1%
1.57 mg/m ³	-14%*	-6%	-4%
11.6 mg/m ³	-19%*	-36%**	-3%
<u>Females</u> (week 4)			
0.05 mg/m ³	-3%	-1%	-24%**
0.46 mg/m ³	-20%*	+6%	-17%*
1.57 mg/m ³	-27%**	-10%*	-20%*
11.6 mg/m ³	-43%**	-39%**	-37%**

* statistically significantly different from control ($p \leq 0.05$); ** ($p \leq 0.01$).

No evidence of a dose-response effect for diazinon is seen for males in this study. However, a dose-response for inhibition of both erythrocyte and brain acetylcholinesterase occurred in the females at the 1.57 and 11.6 mg/m³ levels. A NOAEL of 0.46 mg/m³ for inhibition of neural acetylcholinesterase is used for the derivation of the MRL.

Dose end point used for MRL derivation:

NOAEL LOAEL

Uncertainty factors used in MRL derivation:

1 3 10 (for use of a LOAEL)
 1 3 10 (for extrapolation from animals to humans)
 1 3 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

If so, explain: NA

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

These conversion factors were taken from Interim Methods for Development of Inhalation Reference

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Concentrations, Appendix H (EPA 1990). Inhibition of brain acetylcholinesterase is considered an Extrarespiratory effect.

The Mass Median Aerodynamic Diameter (MMAD) was reported as a lower limit of 0.8 μm and an upper limit of 1.2 μm for an average of 1.0 μm (pg 33 Hartman 1990). The Geometric Standard Deviation (GSD) was reported as a lower limit of 1.2 μm and an upper limit of 1.5 μm for an average of 1.35 or 1.4 μm . The Regional Deposited Dose Ratio (RDDR) from Table H1 under the ER (Extrarespiratory effects) column is 0.0076. This ratio is adjusted by the body weight ratio between humans and female rats (0.166 kg reported). Thus: $\text{RDDR}_{[\text{ADJ}]} = 0.0076 \times (70 \text{ kg}/0.166 \text{ kg})$ (EPA 1988 values for human body weight) = 3.2048

Using Equation 4-7 and 0.0076 for RDDR_{ER} in Table H-1 (MMAD = 0.1, Sigma g = 1.4) in EPA (1990 - Interim Methods for Development of Inhalation Reference Concentrations), and correcting by the body weight ratios, the $\text{NOAEL}_{[\text{HEC}]}$ is calculated:

$$\text{NOAEL}_{[\text{HEC}]} = \text{NOAEL}_{[\text{ADJ}]} \times \text{RDDR}_{\text{ER}}$$

$$\text{NOAEL}_{[\text{HEC}]} = (0.46 \text{ mg}/\text{m}^3 \times 6 \text{ hr}/\text{d}/24 \text{ hr} \times 5 \text{ d}/7 \text{ d}) \times (0.0076 \times 70 \text{ kg}/0.166 \text{ kg})$$

$$\text{NOAEL}_{[\text{HEC}]} = 0.082 \text{ mg}/\text{m}^3 \times 3.2048$$

$$\text{NOAEL}_{[\text{HEC}]} = 0.2628 \text{ mg}/\text{m}^3$$

Thus,

$$\text{MRL} = \text{NOAEL}_{[\text{HEC}]} \div \text{UF}$$

$$\text{MRL} = 0.2628 \text{ mg}/\text{m}^3 \div (3 \times 10)$$

$$\text{MRL} = 0.2628 \text{ mg}/\text{m}^3 \div 30$$

$$\text{MRL} = 9 \times 10^{-3} \text{ mg}/\text{m}^3 = 0.009 \text{ mg}/\text{m}^3$$

Was a conversion used from intermittent to continuous exposure?

If so, explain: Yes. Exposure was for 21 days, 6 hours a day 5 days a week.

$$\text{NOAEL}_{[\text{ADJ}]} = (0.46) \times (6 \text{ hours a day}/24 \text{ hours}) \times (5 \text{ days}/7 \text{ days}) = (0.082 \text{ mg}/\text{m}^3)$$

Other additional studies or pertinent information that lend support to this MRL:

This is the only available well conducted intermediate-duration inhalation study for diazinon. In an acute-duration study in which rats were exposed to 2,300 mg/m^3 diazinon for four hours (Holbert 1989), mild signs of organophosphate toxicity were noted (nasal discharge, salivation). NIOSH recommends an occupational exposure level of 0.1 mg/m^3 , approximately 100-fold higher than the MRL.

Agency Contact (Chemical Manager): Alfred Dorsey

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Diazinon
CAS number(s): 333-41-5
Date: August 1996
Profile Status: Final
Route: [] Inhalation [x] Oral
Duration: [] Acute [x] Intermediate [] Chronic
Key to figure: 64
Species: Dog

MRL: 0.0002 [x] mg/kg/day [] ppm [] mg/m³

Reference: Barnes TB (1988) 90-Day oral toxicity study in dogs. Unpublished report submitted by Ciba-Geigy, Summit NJ dated August 4, 1988. EPA 40815004.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): The purpose of this study was to determine the 13-week oral toxicity profile of diazinon in male and female beagle dogs. Diazinon was added to standard canine ration at concentrations of 0, 0.1, 0.5, 150, and 300 ppm. The test substance was the MG-8 formulation of diazinon (87.7% pure) mixed with feed and adjusted for purity. The concentrations of diazinon in the feed were determined during weeks 1, 3, 5, 9, and 13. Each dog was supplied with approximately 400 g of food daily. The corresponding doses, in mg/kg, were calculated by the authors to be 0.0034, 0.02, 5.9, and 10.9 in males and 0.0037, 0.021, 5.6, and 11.6 in females. Four dogs per sex were assigned to each dose level. After receipt, dogs were allowed approximately six weeks to acclimate. During the acclimation period, body weight and food consumption were measured, and clinical laboratory measurements (hematology, serum chemistry, and urinalysis) and physical, auditory, and ophthalmoscopic exams were performed. Upon initiation of the study, appearance, mortality and clinical observations were monitored daily, while body weight and food consumption were monitored weekly; clinical laboratory measurements were performed at weeks 5 and 9. Physical, auditory, and ophthalmoscopic exams and clinical laboratory measurements were performed prior to termination. A complete necropsy was performed on all animals, and the following organs were collected for histopathological examination: adrenals, brain (cerebral cortex, cerebellar cortex, medulla/pans), epididymides, heart, kidneys, liver, lungs, ovaries, peripheral (sciatic) nerve, pituitary, prostate, salivary (mandibular), spinal cord (cervical, lumbar, thoracic), spleen, testes, thymus, thyroid (with parathyroids), and uterus. After being weighed, a portion of each brain was utilized for determining levels of acetylcholinesterase activity by a calorimetric method. Tissue samples were preserved for subsequent histological examination.

Effects noted in study and corresponding doses:

No deaths occurred during the study. Treatment-related reductions in body weight gain of 34 and 33%, respectively, were noted in the 5.6 mg/kg females and 10.9 mg/kg males, respectively. Clinical signs included emesis and diarrhea, but were not dose related. No pathology of any nervous system tissue (brain, spinal cord, sciatic nerve) was noted under either gross or microscopic examination.

Statistically significant, dose-related decreases in serum cholinesterase levels (marker for exposure to diazinon) were noted in males and females beginning at doses of 0.02 and 5.6 mg/kg, respectively. Significant reductions in erythrocyte and brain acetylcholinesterase levels were noted in males and

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females beginning at the 5.9 and 5.6 mg/kg levels. No change was observed in blood drawn on day 12. On days 29, 56, and 86 erythrocyte acetylcholinesterase declined by 26, 25, and 25% in males and 31, 31, and 31% in females (pp 202–204 for males, pp 257–259 for females). Levels in the highest dose group were similar. Brain samples analyzed at the termination of the study showed reduction of acetylcholinesterase activity of 31% in males at 5.9 mg/kg/day and 42% at 10.9 mg/kg/day. Female brain acetylcholinesterase activity was reduced 30% at 5.6 mg/kg/day and 45% at 11.6 mg/kg/day.

Effect of Diazinon on Cholinesterase Activity (mUnits/mL)

Dose (mg/kg/day)	Serum ChE	Erythrocyte AChE	Brain AChE
Males (Day 86)			
0	2199.5	2950	2067.5
0.0034	1809 (-18%)	3025 (+3%)	1982.5 (-4%)
0.02	1536 (-30%)*	2425 (-18%)	2150 (+4%)
5.9	430.5 (-80%)**	2225 (-25%)**	1432.5 (-31%)**
10.9	335.75 (-85%)**	2025 (-31%)**	1195 (-43%)**
Females (Day 86)			
0	2137.5	3075	2056.7
0.0037	2237.25 (+5%)	3075 (0%)	2137.5 (+4%)
0.021	1824.75 (-15%)	2950 (-4%)	2110 (+3%)
5.6	398.25 (-81%)**	2125 (-31%)**	1442.5 (-30%)**
11.6	355.75 (-83%)**	2125 (-31%)**	1130 (-45%)**

* significantly different from control ($p \leq 0.05$); ** ($p \leq 0.01$)

A NOAEL of 0.02 mg/kg/day is apparent for the neurological endpoint of brain AChE inhibition in both males and females.

Dose endpoint used for MRL derivation:

[x] NOAEL [] LOAEL

MINIMAL RISK LEVEL (MRL) WORKSHEETUncertainty factors used in MRL derivation:

1 3 10 (for use of a LOAEL)

1 3 10 (for extrapolation from animals to humans)

1 3 10 (for human variability)

MRL = NOAEL / UF

MRL = 0.02 mg/kg/day / 100

MRL = 0.0002 mg/kg/day

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

If so, explain: NA

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

Was a conversion used from intermittent to continuous exposure?

If so, explain: NA

Other additional studies or pertinent information that lend support to this MRL:

This study, along with the Singh (1988) study in rats, are the best available for intermediate-duration oral exposure in laboratory animals. A dose-response relationship was demonstrated for inhibition of the neurological target of diazinon, neural acetylcholinesterase. A NOAEL of 0.019 mg/kg/day was also determined in mongrel dogs in a 12-week oral-exposure study (Williams et al. 1959).

Agency Contact (Chemical Manager): Alfred Dorsey

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, and EPA's estimated range associated with an upperbound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

- (1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

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- (2) Exposure Period Three exposure periods - acute (less than 1.5 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the “System” column of the LSE table (see key number 18).
- (4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 “1%” data points in Figure 2-1).
- (5) Species The test species, whether animal or human, are identified in this column. Section 2.4, “Relevance to Public Health” covers the relevance of animal data to human toxicity and Section 2.3, “Toxicokinetics,” contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.
- (7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. “Other” refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.
- (8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.0005 ppm (see footnote “b”).
- (9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into “Less Serious” and “Serious” effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) Reference The complete reference citation is given in chapter 8 of the profile.

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- (11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote “b” indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.0005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale “y” axis. Inhalation exposure is reported in mg/m³ or ppm and oral exposure is reported in mg /kg/day.
- (16) NOAEL In this example, 18, NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.0005 ppm (see footnote “b” in the LSE table).
- (17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.
- (18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk-levels are derived from the EPA’s Human Health Assessment Group’s upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q₁*).
- (19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 →

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 →	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5d/wk 6hr/d	Resp	3 ^b	10 (hyperplasia)	Nitschke et al. 1981

CHRONIC EXPOSURE							
						11	
						↓	
	38	Rat	18 mo 5d/wk 7hr/d			20 (CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5d/wk 6hr/d			10 (CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5d/wk 6hr/d			10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

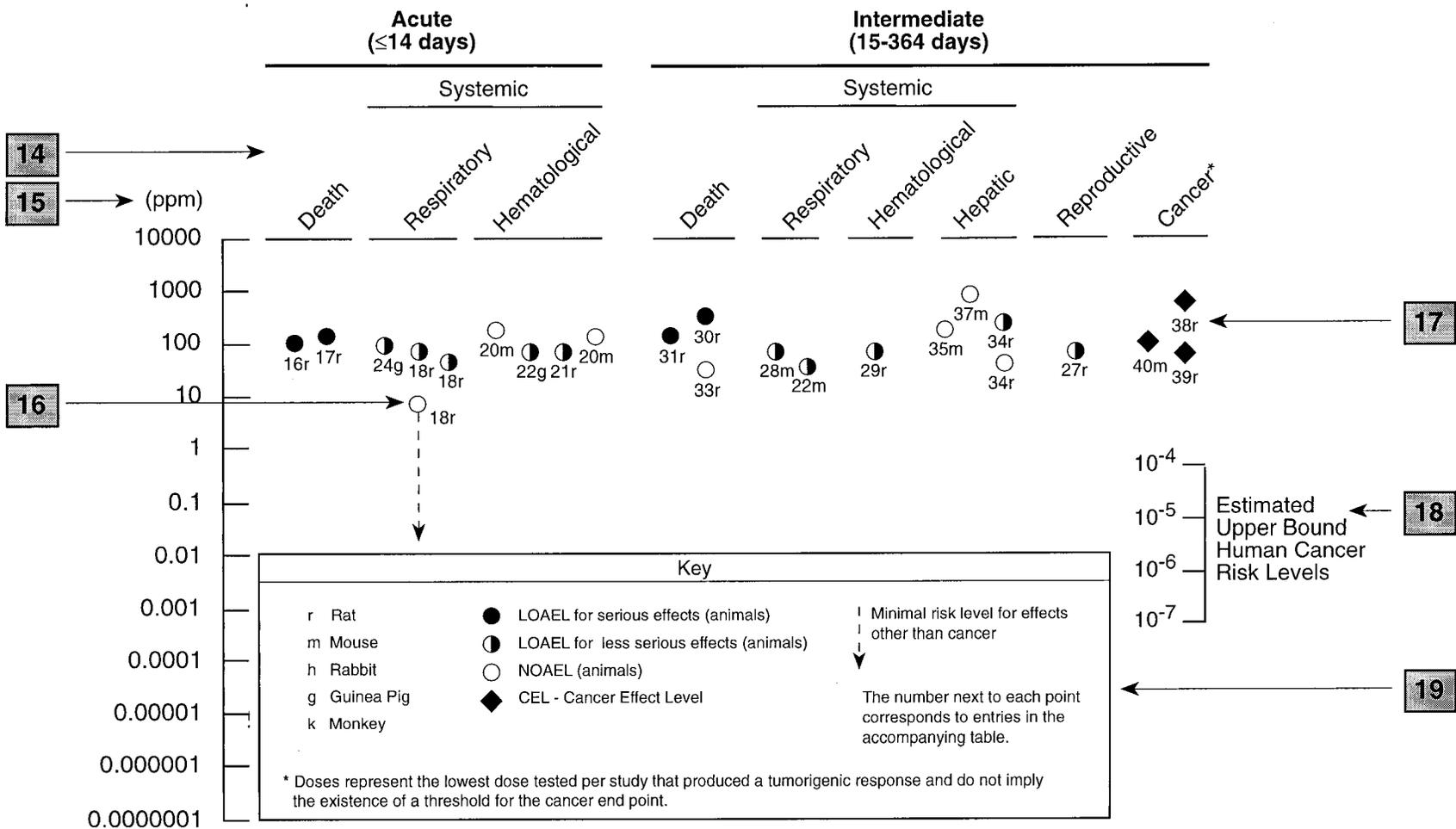
12 →

^a The number corresponds to entries in Figure 2-1.

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

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



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Chapter 2 (Section 2.5)**Relevance to Public Health**

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.7, "Interactions with Other Substances," and 2.8, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

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To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F ₁	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
K _d	adsorption ratio
kg	kilogram
kgg	metric ton
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient

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L	liter
LC	liquid chromatography
LC _{Lo}	lethal concentration, low
LC ₅₀	lethal concentration, 50% kill
LD _{Lo}	lethal dose, low
LD ₅₀	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio

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STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram