PRIORITY DATA NEEDS FOR DIAZINON

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NOTE TO THE READER

The Priority Data Needs documents are intended to characterize substance-specific priority data needs determined via the ATSDR Decision guide for identifying substance-specific data needs related to toxicological profiles (54 Federal Register 37618, September 11, 1989). The identified priority data needs reflect the opinion of the Agency, in consultation with other federal programs, of the research necessary for fulfilling its statutory mandate under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (Superfund) or CERCLA. They are not intended to represent the priority data needs for any other program.

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Prepared by: Agency for Toxic Substances and Disease Registry/
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I. Executive Summary

Diazinon is included in the priority list of hazardous substances identified by ATSDR (ATSDR 2007). This list contains substances that have been identified at National Priorities List (NPL) sites and determined to pose a human health risk based on (1) known or suspected human toxicity, (2) frequency of occurrence at NPL sites or other facilities, and (3) the potential for human exposure to the substance. An updated Toxicological Profile for Diazinon was published by ATSDR in September 2008.

Diazinon (CAS number 333-41-5) is an organophosphorus pesticide. Pure diazinon exists as a colorless liquid. Technical grades appear as a pale to light-brown liquid with a faint ester-like odor. Diazinon may be formulated as granules, a wettable powder, an emulsifiable solution, a dust, a seed dressing, or a mixed formulation with other insecticides. Diazinon is poorly soluble in water, but is soluble in most organic solvents. It has been shown to volatilize from both water and soil media and to decompose at temperatures above 120 °C.

Diazinon was first developed as an insecticide, acaricide, and nematicide for use on a variety of pests for control of soil insects and pests of fruits, vegetables, and forage and field crops. Currently, there is only one producer of diazinon in the United States. In 1990, the United States produced 4.67 million kg; more recent production volume data are not available. Approximately 4 million pounds of active ingredient diazinon are used annually on agricultural sites. In addition to applications in agriculture, diazinon was formerly used extensively in home and garden applications. However, due to the emerging health and ecological risks posed by diazinon,

manufacturers agreed to phase out and cancel all residential products. As a result, the EPA has phased out all residential uses of diazinon as of December 2004.

Diazinon's production and use will result in its release to the environment. Diazinon released to surface waters or soil is subject to volatilization, photolysis, hydrolysis, and biodegradation. 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. The half-life of diazinon in soil is influenced by pH and soil type, with measured values ranging from 14 to 209 days. Diazinon is moderately mobile in soils and can leach from soil into groundwater. Oxypyrimidine is the main soil and water degradate of diazinon. In the atmosphere, diazinon is expected to exist in both the vapor and particulate phases. Particulate-phase diazinon is removed from the atmosphere by wet and dry deposition. Vapor-phase diazinon is rapidly degraded by photochemically-produced hydroxyl radicals, with the half-life for this reaction estimated as 4 hours. Vapor-phase diazinon in the atmosphere is also subject to direct photolysis. The main oxidation product of diazinon in the atmosphere is diazoxon. Bioconcentration in aquatic organisms is low.

The general population may be exposed to diazinon through ingestion of contaminated food or drinking water and inhalation. Ingestion of foods contaminated with small residues of diazinon is the most likely route of exposure for the general population not living in areas where diazinon is extensively used. Populations living within or very near areas of heavy agricultural diazinon use would have increased risk of exposure to relatively larger amounts of diazinon via all natural exposure routes (inhalation, oral, dermal). The dermal and inhalation exposure routes present the greatest potential for significant occupational hazard.. Populations residing near waste disposal sites may be exposed to diazinon in drinking water obtained from groundwater wells due to the potential for diazinon to leach into groundwater, especially near landfills. The potential for significant exposure to diazinon may be higher in small children due to dermal contact and oral ingestion of residues that may be present in soil and dust.

The principal toxic effect of diazinon in humans and animals is inhibition of acetylcholinesterase (AChE), which results in the accumulation of acetylcholine at acetylcholine receptors leading to overstimulation of nerves and muscles. High-level exposure to diazinon causes severe AChE inhibition that may be manifested in 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). Numerous animal studies have assessed diazinon-induced red blood cell (RBC) and/or brain AChE inhibition as a particularly sensitive indicator of both exposure and effect. RBC AChE inhibition can be used as an indicator of a neurotoxic effect because RBC AChE is chemically identical to neural AChE. Most animal studies employed the oral exposure route. Limited animal data indicate that inhalation or dermal exposure to diazinon can result in neurotoxicity similar to that observed following oral exposure. Diazinon does not appear to be a reproductive toxicant. There is some indication that *in utero* exposure to diazinon could cause neurological deficits and delayed development of reproductive and immune systems. Available data indicate that ingested diazinon is not of particular carcinogenicity concern; the carcinogenicity of diazinon has not been assessed via the inhalation or dermal exposure routes.

On the basis of the available data, ATSDR has identified the following priority data needs:

Exposure

- No priority data needs have been identified

Toxicity

- Developmental toxicity data via oral exposure

II. Introduction: ATSDR's Substance-Specific Applied Research Program

A. Legislative

Section 104(i)(5) of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) 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 cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects. Such

program shall include, to the extent necessary to supplement existing information, but shall not be limited to--

- laboratory and other studies to determine short, intermediate, and long-term health effects;
- laboratory and other studies to determine organ-specific, site-specific, and system-specific acute and chronic toxicity;
- laboratory and other studies to determine the manner in which such substances are metabolized or to otherwise develop an understanding of the biokinetics of such substances; and
- where there is a possibility of obtaining human data, the collection of such information.

Section 104(i)(5)(C): In the development and implementation of the research program ATSDR is required to coordinate with EPA and NTP to avoid duplication of research being conducted in other programs and under other authorities.

Section 104(i)(5)(D): It is the sense of Congress that the costs for conducting this research program be borne by private industry, either under the Toxic Substances Control Act (TSCA), the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), or cost recovery under CERCLA.

B. Impact on Public Health

The major purpose of this research program is to supplement the substance-specific informational needs of the public and the scientific community. More specifically for ATSDR, this program will supply necessary information to improve the database to conduct public health assessments. This is more fully described in the ATSDR Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (54 Federal Register 37618) [henceforth referred to as the ATSDR Decision Guide].

Experience from ATSDR health assessments shows the need for more information for select substances, on both exposure and toxicity, so the Agency can more completely assess human health effects. Exposure data collected from this substance-specific research will complement data being collected on a site-specific basis by ATSDR's Division of Health Studies and the Division of Health Assessment and Consultation. More specifically, the Agency will use the exposure data to help identify populations that need follow-up exposure or health-outcome studies.

Regarding substance toxicity, the collected data will be used to characterize the toxicity of the substance for public and scientific community. For ATSDR, the data are necessary and essential to improve the design and conduct of follow-up health studies.

C. Procedures

Section 104(i)(2) of CERCLA, as amended, requires that ATSDR (1) with EPA develop a list of hazardous substances found at NPL sites (in order of priority), (2) prepare toxicological profiles of those substances, and (3) assure the initiation of a research program to fill identified data needs associated with the substances.

The first step in implementing the ATSDR substance-specific research program for diazinon occurred when the data needs for diazinon were determined in the ATSDR Toxicological Profile for Diazinon. Considered a subset of all information gaps on diazinon, these data needs were reviewed by scientists from ATSDR and other federal agencies. They were peer reviewed by an external review panel and made available for public comment. All comments received by ATSDR on the identification of data needs for diazinon were addressed before the toxicological profile was finalized.

The purpose of this paper is to take the data needs identified in the Toxicological Profile for Diazinon and subject them to further scientific evaluation. This will lead to priorities and ultimately to ATSDR's substance-specific research agenda. To affect this step, ATSDR developed and presented a logical scientific approach to priority setting in its Decision Guide.

Briefly, data needs are categorized as exposure or toxicity and are then subcategorized across three levels (Tables 1 and 2). Level I research is a base set of exposure and toxicity information to identify basic characteristics of each substance. Level II research is conducted to confirm the toxicity and exposure indicated by Level I data. Level III research will improve the application of the results of Level II research to people.

The Decision Guide recognized three general principles for setting priorities:

- Not all information gaps identified in toxicological profiles are data needs.
- All data needs are not the same priority.
- Substances should be considered individually, but may be grouped, because of structural similarity or other relevant factors.

Other considerations spelled out in the Decision Guide include:

- All levels of data should be considered in selecting priority data needs.
- Level I gaps are not automatically in the priority grouping. In general, Level I data have priority when there are no higher level data for the same category, and when data are insufficient to make higher level priority testing decisions. For example, priority would generally not be assigned multigenerational animal studies (Level II) if an adequate subchronic study (Level I) had not been conducted that evaluated reproductive organ histopathology.
- Priority for either exposure or toxicity data requires thorough evaluation of research needs in other areas to help achieve a balanced research program for each substance.

The Decision Guide listed the following eight tenets to determine research priorities:

- Development and/or confirmation of appropriate analytical methods.
- Determination of environmental and human exposure levels when analytical methods are available.
- Bioavailability studies for substances of known significant toxicity and exposure.
- Studies available to characterize target organs and dose response.
- Disposition studies and comparative physiologically-based pharmacokinetics when a toxic end point has been determined and differences in species response have been noted.
- Mechanistic studies on substances with significant toxicity and substantial human exposure.
- Investigation of methods to mitigate toxicity for substances when enough is known about mode of action to guide research.
- Epidemiologic studies designed to link human disease with a substance of known significant toxicity.

These last three "prioritizing" tenets address Level III research. When Level III research is identified as priority, ATSDR will not develop detailed methods to successfully fulfill the data

needs. Because there are no standard "testing guidelines" for Level III research, we expect considerable discussion between ATSDR and parties interested in conducting this research. Thus, ATSDR will only announce that its scientists believe that the accumulation of Level III research is appropriate, and it is a priority at this time. ATSDR will state the reasons why this is so.

D. Selection Criteria

ATSDR prepares toxicological profiles on substances that are most commonly found at facilities on the NPL sites and which, in its sole discretion, pose the most significant threat to human health because of their known or suspected toxicity and potential for human exposure.

Briefly, the rationale is as follows:

1. Frequency of Occurrence

***Finding*:** Diazinon is included in the priority list of hazardous substances identified by ATSDR (ATSDR 2007).

Diazinon has been detected in at least 25 of 1,678 National Priorities List (NPL) hazardous waste sites in the United States (HazDat 2006). Exposure to diazinon at these sites may occur by contacting contaminated air, water, soil, or sediment. ATSDR is presently evaluating the extent of media-specific contamination at these and other sites.

2. Potential for Human Exposure

***Finding*:** ATSDR scientists have determined that there has been significant past human exposure and that the potential exists for current human exposure to diazinon via inhalation, ingestion, and skin contact.

The following is a brief summary of the potential for human exposure to diazinon. For a more detailed discussion of available information, refer to the ATSDR Toxicological Profile for diazinon, Chapter 6, on Potential for Human Exposure (ATSDR 2008).

Diazinon is a human-made synthetic chemical that does not occur naturally in the environment. Diazinon (CAS number 333-41-5) is the common name for an organophosphorus pesticide with the active ingredient O,O-diethyl-O-(2-isopropyl-6-methyl-4-pyrimidinyl) phosphorothioate. Pure diazinon exists as a colorless liquid. Technical grades, usually containing 85–90% diazinon, appear as a pale to light-brown liquid with a faint ester-like odor. It may also be formulated as granules, a wettable powder, an emulsifiable solution, a dust, a seed dressing, or a mixed formulation with other insecticides. Diazinon is poorly soluble in water, but is soluble in most organic solvents, such as alcohol, ether, cyclohexane, and benzene. It has been shown to volatilize from both water and soil media. Diazinon decomposes above 120 °C (HSDB 2006).

Diazinon is produced commercially by reacting 2-isopropyl-4-hydroxy-6-methylpyrimidine and O,O-diethyl phosphorochloridothioate (HSDB 2006). It is also produced by condensation of isobutyramidine with acetoacetate to yield the intermediate, 2-isopropyl-4-methylpyrimidine, which is transformed to diazinon by treatment with diethylthiophosphate acid (Müller et al. 2005). Currently, there is only one producer of diazinon in the United States (SRI 2005). In 1990, the United States produced 4.67 million kg (Larkin and Tjeerdema 2000), and this is the final year that production volume data were available. Diazinon was first developed as an insecticide, acaricide, and nematicide, for use on a variety of pests for control of soil insects and pests of fruit, vegetables, and forage and field crops. Approximately 4 million pounds of active ingredient diazinon are used annually on agricultural sites. In addition to applications in agriculture, diazinon has been heavily used in urban areas. It had been used extensively in home and garden applications, in formulations designed to prevent such pests as crickets or cockroaches from infesting homes or offices, and in pet collars. However, due to the emerging health and ecological risks posed by diazinon, manufacturers agreed to phase out and cancel all residential products. As a result, the EPA has phased out all residential uses of diazinon as of December 2004 (EPA 2004).

Diazinon is an important substance for research because of its widespread environmental contamination. According to the Toxic Chemical Release Inventory (TRI), 21 facilities manufactured or processed diazinon in 2004 (TRI04 2006). It was estimated that 13,123 pounds of diazinon, amounting to 55% of the total environmental release, was discharged to land from manufacturing and processing facilities in the United States in 2004 (TRI04 2006). Smaller amounts, 10,287 and 358 pounds, were released to water and air, respectively (TRI04 2006). Diazinon is released to the environment solely by human activities. Releases of diazinon to the

environment may result from its manufacture, use, storage, distribution, and disposal. Diazinon is released to soils primarily from its registered use on various agricultural crops and its former use in home garden and lawn applications. Major atmospheric emissions result from volatilization of the chemical from soil resulting from its extensive use as an insecticide or from drift during pesticide application. Diazinon is released to surface waters directly by point source discharges, from drift during pesticide applications, and by runoff from agricultural and urban areas (EPA 1995a, 1995b).

Diazinon is found in all environmental compartments, but shows no pronounced tendency to partition to a particular environmental compartment primarily because of its relatively rapid degradation in each environmental medium. Given adequate time, diazinon will be degraded by abiotic and biotic processes so that the parent compound is not persistent. 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 degraded 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; EPA 1976; Ferrando et al. 1992; Frank et al. 1991; Scheunert et al. 1993; Schoen and Winterlin 1987; Sharom et al. 1980b). The half-life of diazinon in soil is influenced by the pH conditions in the soil and the soil type, with measured values ranging from 14 to 209 days (Schoen and Winterlin 1987). Diazinon is moderately mobile in soils under certain conditions, particularly soils with an organic matter content <3%, and can leach from soil into groundwater (Arienzo et al. 1994). Oxypyrimidine is the main soil and water degradate of diazinon (EPA 2004). In the atmosphere, diazinon is expected to exist in both the vapor and particulate phases (Eisenreich et al. 1981). Particulate-phase diazinon is removed from the atmosphere by wet and dry deposition. Vapor-phase diazinon is rapidly degraded by photochemically-produced hydroxyl radicals, with the half-life for this reaction estimated as 4 hours (Meylan and Howard 1993). Vapor-phase diazinon in the atmosphere is also subject to direct photolysis. The main oxidation product of diazinon in the atmosphere is diazoxon (Seiber et al. 1993). Measured BCFs in fish for diazinon were generally below 100, suggesting that bioconcentration in aquatic organisms is low (El Arab et al. 1990; Seguchi and Asaka 1981; Tsuda et al. 1995, 1997).

Diazinon has been identified in at least 25 of the 1,678 hazardous waste sites that have been proposed for inclusion on the EPA NPL (HazDat 2006). However, the number of sites evaluated for diazinon is not known. Diazinon has been identified in air samples collected at 1 site, surface water samples collected at 5 sites, groundwater samples collected at 8 sites, soil samples collected at 9 sites, and sediment samples collected at 4 of the 25 NPL hazardous waste sites where it was detected in some environmental medium (HazDat 2006).

The general population may be exposed to diazinon through ingestion of contaminated food or drinking water and inhalation. In order to mitigate the exposure and risk to the general population, especially children, the EPA has phased out all residential uses of diazinon as of December 2004 (EPA 2004). Ingestion of foods contaminated with small residues of diazinon is the most likely route of exposure for the general population not living in areas where diazinon is extensively used. From U.S. Food and Drug Administration (FDA) Total Diet Studies, estimated daily diazinon intakes (μg/kg body weight/day) for total diet analyses reported were 0.0034 and 0.0017 in 1989 (FDA 1990); 0.0022 and 0.0017 in 1990 (FDA 1991); and 0.0022 and 0.0022 in 1991 (FDA 1992) for 14–16-year-old males and 60–65-year-old females, respectively.

Populations living within or very near areas of heavy agricultural diazinon use would have increased risk of exposure to relatively larger amounts of diazinon through dermal contact with contaminated plants, soils, surface waters, and artificial surfaces such as playground equipment or pavements; by inhalation of the mist formed from the applied insecticide; or by ingestion of water or food-borne residues. During EPA's National Human Exposure Assessment Survey conducted to assess residential exposure, diazinon was found in 53% of house dust samples at <0.02–50.5 μg/m^2; indoor air, 63%, <0.002–20.5 μg/m^3; hand wipes, 32%, <0.01–18.4 μg; and foundation soil (2.5 cm depth), 37%, <0.007–7 μg/g (Gordon et al. 1999). In areas of high agricultural diazinon use, inhalation exposure is likely to exceed dietary exposure. The mean air exposure for residents to diazinon in an area of high pesticide use was 1,380 ng/day and dietary exposure was 590–1,140 ng/day (Whitmore et al. 1994).

Drinking water facilities are not required to monitor for diazinon and, therefore, only limited data are available. EPA's Water Resources Assessment estimated diazinon acute exposures in drinking water were 2.3–22, 3.0–22, and 0.90 μg/L based on agricultural and non-agricultural use surface water and groundwater, respectively. The estimated chronic diazinon exposures in drinking water were 0.19–5.8, 0.46–5.8, and 0.90 μg/L based on agricultural and non-agricultural

use surface water and groundwater, respectively (EPA 1999). In the U.S. Geological Survey's National Water-Quality Assessment Program in 1992–1996, diazinon was detected at a frequency of 1.3% at 2,459 groundwater sites sampled in 20 of the nation's major hydrologic basins with a maximum detected concentration of 0.16 µg/L (Kolpin et al. 2000). Populations residing near waste disposal sites may be subject to higher than average levels of diazinon in drinking water obtained from groundwater wells due to the possibility of diazinon leaching into groundwater, especially near landfills. These populations may also be exposed to diazinon in air since diazinon could be carried in particulates and as a vapor through wind or anthropogenic activities. However, data of exposures of residents living near hazardous waste sites through inhalation of air or ingestion of drinking water could not be located.

Children are expected to be exposed to diazinon by the same route as adults, such as inhalation of contaminated air, ingestion of contaminated groundwater used as a source of drinking water, ingestion of contaminated food, and dermal contact with soils and contaminated surfaces. The primary route of exposure for children is through the diet. From FDA Total Diet Studies (July 1986–April 1991), it was reported that the mean daily intake of diazinon residues in foods thought to be in the diets of infants and children were 0.0061µg/kg/day for the 6–11-month-old group, 0.0106 µg/kg/day for the 2-year-old group, 0.0037 µg/kg/day for the 14–16-year-old female group, and 0.0052 µg/kg/day for the 14–16-year-old male group (Gunderson 1995). Small children are more likely to be exposed to diazinon through dermal contact and oral ingestion of residues that may be present in soil and dust, due to increased hand-to-mouth activity and playing habits. The Minnesota Children's Pesticide Exposure Study (MNCPES) detected diazinon in 10% of carpet and surface samples collected from the homes of 102 children, ages 3–13, and reported diazinon detection in 6 of 94 hand rinse samples collected (Lioy et al. 2000). In another study, house dust samples collected from homes in rural California contained diazinon concentrations ranging from 0.2 to 169 mg/kg and diazinon residues of 220, 125, and 52 ng were detected on the hands of 3 of 11 toddlers (Bradman et al. 1997). Children who live near hazardous waste sites or municipal landfills may be exposed to diazinon in drinking water obtained from groundwater wells and air; however, data on the intake by children were unavailable.

Occupational exposures to diazinon occur through dermal contact and inhalation in the workplace where it is produced or used. The National Occupational Exposure Survey (NOES) conducted by

NIOSH from 1981 to 1983 estimated that 39,342 workers (including 3,216 women) employed at 3,168 facilities were potentially exposed to diazinon in the United States (NIOSH 2006).

3. Toxicity

***Finding*:** ATSDR considers that short, intermediate and long term health effects can result from inhalation, ingestion, and dermal contact of diazinon.
Target organs or systems known to be affected include central and peripheral nervous systems and neuromuscular junctions.

The following is a brief summary of the toxicology of diazinon. Refer to the ATSDR Toxicological Profile for diazinon chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 2008).

The principal toxic effect of diazinon in humans and animals is inhibition of AChE, which results in the accumulation of acetylcholine at acetylcholine receptors leading to overstimulation of nerves and muscles. High-level exposure to diazinon causes severe AChE inhibition that may be manifested in muscarinic effects (bronchoconstriction, increased bronchosecretion, nausea and vomiting, diarrhea, bradycardia, hypotension, miosis, urinary incontinence), nicotinic effects (tachycardia, hypertension, muscular twitching and weakness, fasciculation, cramping), and central nervous system effects (anxiety, apathy, depression, giddiness, drowsiness, insomnia, nightmares, headaches, confusion, ataxia, depressed reflex, seizure, respiratory depression, coma). In sufficiently high exposures (accidental or intentional), respiratory and cardiac failure and death may result without timely treatment intervention (Adlakha et al. 1988; Balani et al. 1968; Beane Freeman et al. 2005; Bichile et al. 1983; Cantor et al. 1992; Dagli et al. 1981; Dahlgren et al. 2004; Davis et al. 1993; Hata et al. 1986; Kabrawala et al. 1965; Kamha et al. 2005; Klemmer et al. 1978; Lee 1989; Limaye 1966; Maizlish et al. 1987; Morris et al. 1986; Poklis et al. 1980; Rayner et al. 1972; Reichert et al. 1977; Richter et al. 1992; Schenker et al. 1992; Shankar 1967, 1978; Soliman et al. 1982; Wadia et al. 1974; Wedin et al. 1984; Weizman and Sofer 1992). The cholinergic manifestations of high acute exposure to diazinon in animals include anorexia, ataxia, epistaxis, tremors, listlessness, gasping, convulsions, tachypnea, dyspnea, prostration, fasciculations, twitches, exophthalmos, diarrhea, salivation, diuresis, lacrimation, prostration, Straub tail reflex, and hypothermia (Boyd and Carsky 1969; Chow and Richter 1994; Earl et al. 1971; EPA 1996, 2000; Harris and Holson 1981; Moser 1995; Moser et

al. 2005; Robens 1969). Clinical signs of diazinon neurotoxicity following repeated oral exposure in animals have been reported at doses ranging from 30 to 300 mg/kg/day (Chow and Richter 1994; EPA 2000; Giknis 1989; Harris and Holson 1981; Robens 1969). Limited information is available regarding clinical signs of neurotoxicity in animals exposed to diazinon by inhalation. A single available study reported decreased activity and salivation responses in rats following acute-duration inhalation exposure to diazinon (Holbert 1989). Clinical signs of neurotoxicity were reported in one acute lethality study in rats that were dermally exposed to diazinon (Gaines 1960).

As previously noted, the systemic toxicity of diazinon is mainly attributable to its action on the nervous system. Although AChE is intimately associated with neurotransmission within the central and peripheral nervous system, AChE is also found in RBCs. In animals, measures of RBC AChE activities have been used as indicators of exposure and effect for cholinesterase inhibitors such as diazinon. Decreased activity of RBC AChE is indicative of a potential neurotoxic effect because RBC AChE is identical to neural AChE.

Numerous animal studies identify levels of exposure to diazinon resulting in RBC and/or brain AChE inhibition (Abu-Qare and Abu-Donia 2001; Barnes 1988; Davies and Holub 1980a, 1980b; EPA 1996, 2000; Hartman 1990; Kirchner et al. 1991; Rudzki et al. 1991; Singh 1988). A range of 20–59% RBC and/or brain AChE inhibition is considered to represent a toxicologically significant adverse neurological effect. In the absence of more serious (clinical signs) of neurotoxicity, this range of RBC and/or brain AChE inhibition may represent the most sensitive effect for diazinon toxicity and has been observed in animals following repeated oral exposure at diazinon doses of 0.3–75 mg/kg/day (Barnes 1988; Davies and Holub 1980a, 1980b; EPA 1996, 2000; Kirchner et al. 1991; Rudzki et al. 1991; Singh 1988). A single dermal application in rats at a dose level of 65 mg/kg resulted in 52% RBC AChE inhibition. In a repeated-exposure inhalation study, exposure to an airborne concentration of 1.57 mg/m^3, 6 hours/day, 5 days/week for 3 weeks resulted in 36–39% RBC AChE inhibition in rats (Hartman 1990). RBC AChE appears to be more sensitive than brain AChE to diazinon toxicity (Barnes 1988; Davies and Holub 1980a; EPA 1996; Singh 1988; Timchalk et al. 2005). Following single oral dosing, peak cholinesterase inhibition is typically observed at 6–12 hours (Chow and Richter 1994; Timchalk et al. 2005). Results of longer-term oral studies indicate that diazinon-induced RBC AChE inhibition increases in severity with exposure duration to a peak at approximately 35 days, after which the severity of the inhibition remains relatively constant (Davies and Holub 1980a). Rat

and dog studies indicate that females may be more sensitive than males to diazinon-induced AChE inhibition, particularly with respect to brain AChE inhibition (Barnes 1988; Davies and Holub 1980b; EPA 1996, 2000; Singh 1988). Diazinon-induced neurohistopathological effects have not been demonstrated.

The potential reproductive toxicity of diazinon has not been extensively studied. No human data are available; animal data consist mainly of repeated-dose oral studies that found no histopathologic evidence of treatment-related effects in reproductive tissues at exposure levels up to and including those resulting in clinical signs of neurotoxicity. No human data are available regarding the potential for diazinon-induced developmental toxicity. Limited animal data indicate the potential for diazinon-induced neurological deficits and delayed development of reproductive tissues and immunological function following *in utero* exposure (Barnett et al. 1980; Spyker and Avery 1977). There is limited evidence of morphological changes in spleen, thymus, and lymph nodes of animals following oral exposure to relatively high doses of diazinon (Boyd and Carsky 1969), but no studies have demonstrated compromised immunological function. Predominantly negative results have been reported in testing of diazinon for genotoxicity. Two epidemiological studies reported weak associations between exposure to diazinon and lung cancer. Results of a few case-control studies have suggested possible links between diazinon exposure and non-Hodgkin's lymphoma, multiple myeloma, and childhood brain cancer. However, all of these studies involved exposure to other pesticides as well. The National Cancer Institute (NCI 1979) concluded that diazinon was not carcinogenic to either sex of rats or mice receiving diazinon in the diet for 2 years, including exposure levels that elicited clinical manifestations of neurotoxicity. No studies have assessed the carcinogenicity of diazinon following inhalation exposure. The Department of Health and Human Services (DHHS) and the International Agency for Research on Cancer (IARC) have not classified diazinon as to its carcinogenicity. The EPA Drinking Water Standards and Health Advisories (EPA 2006) includes a cancer Group E (evidence of noncarcinogenicity in humans) designation for diazinon. There is no assessment for diazinon on EPA's Integrated Risk Information System (IRIS).

III. Identification of Data Needs

In evaluating the exposure and toxicity testing needs for diazinon, ATSDR considered all available published and unpublished information that has been peer-reviewed. From its evaluation of these data, ATSDR is recommending the conduct of specific research or testing.

A. Exposure Data Needs (Table 1)

Three of the eight "prioritizing" tenets presented in the Decision Guide directly address exposure data needs:

- Development and/or confirmation of appropriate analytical method;
- Determination of environmental and human exposure levels when analytical methods are available; and
- Bioavailability studies for substances of known significant toxicity and exposure.

The progressive accumulation of exposure information begins with developing suitable analytical methods to analyze the compound in all relevant biological and environmental media, followed by confirmation of exposure information, before the conduct of any Level III research. However, in order to know what analytes are available to monitor, some basic environmental fate information is generally required and becomes a priority if it is lacking.

Bioavailability and food chain bioaccumulation studies are appropriately placed in Level II, and should be undertaken after analytical methods are developed and the substance has been confirmed at many hazardous waste sites and in environmental media.

1. Levels I & II Data Needs

a. Analytical Methods

***Purpose*:** To determine if available methods are adequate to detect and quantify levels of diazinon in environmental and biological matrices. The methods should be sufficiently specific and sensitive to measure (1) background levels in the environment and the population; and (2) levels at which biological effects might occur.

***Finding*:** A data need has been identified. Additional methods are needed for the quantitative analysis of diazinon transformation products in environmental matrices and metabolites in blood samples. The development of analytical methodology for the identification and quantification of the transformation products and metabolites is required to properly evaluate the presence and

effects of diazinon in environmental and biological samples. Since diazinon degrades relatively rapidly in each environmental medium, the potential exists for human exposure to the transformation products, which could present similar toxicity or even higher toxicity than the parent compound. Populations residing near waste disposal sites may be subject to higher than average levels of diazinon transformation products in drinking water obtained from groundwater wells due to the possibility of diazinon and its transformation products leaching into groundwater, especially near landfills. While analytical methods for the quantification of diazinon metabolites in urine do exist, further studies designed to refine the identification of metabolites specific to diazinon in blood and provide dosimetric data would be useful in the search for a more dependable biomarker of diazinon exposure.

Analytical methods exist for the detection of diazinon in human biological samples and environmental media. These methods are sufficiently sensitive and reliable enough to measure background levels in the general population as well as levels at which health effects might occur after short- and long-term exposure. Since diazinon is rapidly metabolized, determination of the parent compound in biological samples can only provide evidence of very recent exposures. Analytical methods have been established for the determination of diazinon metabolites.

Common methods for measuring diazinon and its metabolites in biological media include gas chromatography (GC) using a flame photometric detector (FPD), a mass spectroscopy (MS) detector, an electron capture detector (ECD), or a flame ionization detector (FID). The preparation of samples usually involves variations of solid-phase extraction and/or liquid/liquid extraction with organic solvents. Methods exist for the detection of diazinon in blood (Garcia-Repetto et al. 2001), serum (Liu et al. 1994), human tissues (Kirkbride 1987; Poklis et al. 1980), and animal fat and tissue (Brown et al. 1987; Holstege et al. 1991). Methods also exist for the detection of diazinon metabolites in urine (Olsson et al. 2003; Reid and Watts 1981; Yokley et al. 2000). Detection limits in the ppb to ppm range with recoveries of ≥88% have been reported for blood samples (Garcia-Repetto et al. 2001; Musshoff et al. 2002). Sensitivity for diazinon in serum was reported to be 1.8 pg; however, no data on overall recoveries were provided (Liu et al. 1994). In urine, diazinon metabolites had detection limits in the ppb to ppm range with recoveries of ≥96% (Olsson et al. 2003; Reid and Watts 1981; Yokley et al. 2000). No limits of detection or recovery data were provided for human tissue (Kirkbride 1987; Poklis et al. 1980). Detection limits of 0.01–0.05 ppm and recoveries of 88 and 95% were reported for bovine liver and rumen content samples, respectively (Holstege et al. 1991).

Commonly used methods for detecting diazinon in environmental samples are GC or high-performance liquid chromatography (HPLC), in conjunction with an MS detector, an NPD, or an FPD. Sample preparation methods vary depending on the sample matrix. Methods exist for measuring the concentration of diazinon in air (Hsu et al. 1988; NIOSH 1994; OSHA 1986; Williams et al. 1987), drinking water (Driss et al. 1993; EPA 1995a; Kwakman et al. 1992), groundwater (EPA 1995b), surface water (Kwakman et al. 1992; Mattern et al. 1991), waste water (EPA 1993a, 1993b), sediment (USGS 2002a), soil (Burkhard and Guth 1979; Lopez-Avila et al. 1985), fruits, vegetables, crops, and prepared foods (AOAC 1990a, 1990b, 1990c; Bicchi et al. 1997; Hopper 1988; Hsu et al. 1991; Kadenczki et al. 1992; Leoni et al. 1992; Liao et al. 1991), and cow's milk (Di Muccio et al. 1996; Toyoda et al. 1990). Detection sensitivities and recoveries ranged from 30 ppt to 0.2 ppm and 70–103%, respectively in various foods and 10 ppb and 84–88%, respectively in cow's milk. Diazinon was measured with detection limits in the ppm to ppb range and recoveries of ≥73% in air. Sensitivity of detection and recoveries, respectively, for different water samples were as follows: drinking water: 0.03–20 ppb and 83–95%; groundwater: 0.13 ppb and 94%; surface water: 0.5 ppt–50 ppb and 95–104%; and waste water: 0.012–0.6 ppb and 67–94%. Methods for measuring diazinon in soils and sediment are capable of detection sensitivities of 1.24–4 ppb and provide recoveries ranging from 71 to 103%. The sensitivity of the methods for detecting diazinon in air, water, soil, and food and beverages are sufficient for measuring both background levels and higher levels of acute exposure.

***Priority Recommendation*:** The identified data need is not considered priority. Whereas a need exists to have routine methods to quantify diazinon transformation products in environmental media and metabolites in blood samples, methods are available to quantify the parent compound, diazinon. Methods of analysis for the elucidation and confirmation of transformation products and metabolites of diazinon in environmental and biological samples are available. Also, methods of detection and quantification of metabolites in urine have been reported.

b. Physical/Chemical Properties

***Purpose*:** To determine whether adequate data on the chemical and physical properties of diazinon are available to permit estimation of its environmental fate under various conditions of release, and evaluation of its pharmacokinetics under different exposure durations and routes.

***Finding*:** A data need has been identified. The relevant physical and chemical properties of diazinon, including water solubility (HSDB 2006), vapor pressure (HSDB 2006; O'Neil et al. 2001), K_{ow} (HSDB 2006), K_{oc} (HSDB 2006), and Henry's law constant (HSDB 2006), have either been measured experimentally or have been estimated accurately enough to permit the evaluation of the environmental fate and transport of diazinon. However, there are data gaps for physical and chemical properties of toxic diazinon degradation products.

***Priority Recommendation*:** The identified data need is not considered priority. Whereas a need exists for physical and chemical properties data for diazinon degradation products, physical and chemical properties for diazinon itself have been adequately assessed.

c. Exposure Levels

(1) Environmental Media

***Purpose*:** To determine whether adequate data are available on the levels of diazinon in the ambient and contaminated environments for purposes of conducting meaningful follow-up exposure and health studies.

Finding: A need to obtain reliable and current data on concentrations of diazinon in contaminated environmental media at hazardous waste sites has been identified.

In ambient air samples collected in 14–16 states, diazinon was detected in 50% of the 2,479 samples analyzed with a mean concentration of 2.5 ng/m^3 and a maximum concentration of 62.2 ng/m^3 (Kutz et al. 1976). Nationwide, diazinon was detected in 48% of 123 urban air samples collected in 10 U.S. cities, with a maximum reported concentration of 23 ng/m^3 and a mean of 2.1 ng/m^3 (Carey and Kutz 1985). The estimated mean diazinon concentrations detected in outdoor air in Jacksonville, Florida and Springfield, Massachusetts were 1.1–13.8 and 8.2–9.2 ng/m^3, respectively (Whitmore et al. 1994). The estimated diazinon concentrations detected in indoor air in these cites were 85.7–420.7 and 2.5–48.4 ng/m^3, respectively (Whitmore et al. 1994). Diazinon concentrations in air and fog water samples measured near areas of agricultural use ranged from 0.013–10 ng/m^3 (Majewski et al. 1998; Zabik and Seiber 1993) and 0.13–18 µg/L (Schomburg et al. 1991), respectively. Ambient air sampled within 800 m of two pesticide formulation plants in Arkansas and within 275 m of a pesticide formulation plant in

Tennessee contained diazinon concentrations of 0.3–18 and 0.5–27.9 ng/m^3, respectively (Lewis and Lee 1976). Greenhouse air after spray and fog applications of an emulsifiable concentrate of diazinon contained concentrations of up to 297 and 3,030 µg/m^3, respectively (Lenhart and Kawamoto 1994). Populations residing near hazardous waste sites may be subject to above average levels of diazinon in the ambient air. Diazinon has been detected in air samples collected at 1 of the 25 NPL hazardous waste sites where diazinon was detected in some environmental medium (HazDat 2006).

In a national surface water monitoring program, diazinon was detected in only 1.2% of samples collected and the maximum concentration reported was 2.38 µg/L (Carey and Kutz 1985). Diazinon has been measured in surface water with concentrations ranging from 1.1 to 169 ng/L (Maguire and Tkacz 1993; Pereira and Hostettler 1993; USGS 2002b). The maximum and average diazinon concentrations measured in 1,243 rural and urban stream surface water samples collected in Texas decreased from 2.58 and 0.32 µg/L, respectively, in 2001 to 0.85 and 0.04 µg/L, respectively, in 2004, indicating that the phasing out of residential uses of diazinon has led to a decrease in surface water occurrences (Banks et al. 2005). Water samples collected from irrigation ditches near areas of high agricultural use contained diazinon concentration of up to 259 ng/L (Li et al. 2002). Diazinon has been detected at a frequency of 1.3% at 2,459 ground-water sites sampled in 20 of the nation's major hydrologic basins with a maximum detected concentration of 0.16 µg/L (Kolpin et al. 2000). Diazinon was detected with maximum and mean concentrations of 478 and 162 µg/L, respectively, in Mississippi in an area where appreciable agricultural use occurs. Diazinon has been detected in surface water and groundwater samples collected at 5 and 8 of the 25 NPL hazardous waste sites, respectively, where diazinon was detected in some environmental medium (HazDat 2006). A maximum diazinon residue of 1.7 mg/L was detected in publicly owned treatment works (POTW) effluents (Burkhard and Jenson 1993). EPA's Water Resources Assessment estimated diazinon acute exposures in drinking water were 2.3–22, 3.0–22, and 0.90 µg/L based on agricultural and non-agricultural use surface water and groundwater, respectively. The estimated chronic diazinon exposures in drinking water were 0.19–5.8, 0.46–5.8, and 0.90 µg/L based on agricultural and non-agricultural use surface water and groundwater, respectively (EPA 1999). Diazinon was detected in 5 of 53 residential drinking wells at an average concentration of 0.02 µg/L in a town in Connecticut which relies on groundwater for its potable water source (Eitzer and Chevalier 1999). No diazinon was detected in 1,349 wells sampled in 38 states during EPA's National Survey of Pesticides in drinking water (EPA 1999). Populations residing near waste disposal sites may be

subject to higher than average levels of diazinon in drinking water obtained from groundwater wells due to the possibility of leaching into groundwater, especially near landfills.

Concentrations of diazinon in sediments have been reported as ranging from not detected to 2.8 ng/g (Domagalski and Kuivila 1993). In a national monitoring study, diazinon was detected in 0.5% of sediment samples analyzed, with a maximum concentration of 7.1 µg/L (Carey and Kutz 1985). Diazinon concentrations in soils and sediments sampled near areas of agricultural use ranged from 1 to 3,307 and from 0.5 to 38 µg/kg, respectively (Baum et al. 2001; Sapozhnikova et al. 2004; Wan et al. 1994). Diazinon residues have been measured as high as 95.5 and 35.6 mg/m^2 in soils collected 2 and 14 days after application (Glotfelty et al. 1990b), respectively, and 21 µg/g (wet weight) in sediments of irrigation ditches collected 4 days post-application (Szeto et al. 1990). Diazinon has been detected in soil and sediment samples collected at 9 and 4 of the 25 NPL hazardous waste sites, respectively, where diazinon was detected in some environmental medium (HazDat 2006).

Diazinon concentrations measured in tissues of fish collected from a creek ranged from 17 to 92 µg/g (Braun and Frank 1980). Diazinon residues were found in the muscle, liver, gonads, and gills of fish collected from the Salton Sea, an agricultural drainage reservoir in California, at mean concentrations ranging from 2.4 to 17.2 ng/g wet weight (Sapozhnikova et al. 2004).

Diazinon was detected in 894 samples of 144 different ready-to-eat foods monitored from 1982 to 1991at a mean concentration of 0.0019 µg/g in the FDA's Revised Market Basket Survey (KAN-DO Office and Pesticides Team 1995). In the EPA's Revised Organophosphate Pesticides Cumulative Risk Assessment, monitoring data on diazinon in various foods sampled for the years 1994–2000 were reported with mean concentrations ranging from not detected to 0.0012 ppm (EPA 2002). FDA Total Diet Studies analyses on various meats sampled for the years 1991–1999 found mean diazinon residue concentrations ranging from 0.0008 to 0.009 mg/kg (EPA 2002). Residues of diazinon in levels of 0.005–0.586 mg/L have been reported in milk (Salas et al. 2003).

***Priority Recommendation*:** The identified need is not considered priority. Reliable and current 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 and the resulting body burden of diazinon can be used to assess the potential risk of adverse health effects in

populations living in the vicinity of hazardous waste sites. However, ATSDR has developed a hazardous substance release/health effects database (HazDat) that includes the extant data for the 25 NPL sites at which diazinon has been found. This database includes maximum concentrations of diazinon in on- and off-site media, and an indication of relevant routes of exposure. Further evaluation of this database is needed first to assess if collection of additional media-specific data is assigned priority.

(2) Humans

***Purpose*:** To determine whether adequate data are available on the levels of diazinon in human tissues for the general population and exposed populations for purposes of conducting meaningful follow-up exposure and health studies.

***Finding*:** A need has been identified. No data are available on the levels of diazinon in body tissues or fluids for people living near hazardous waste sites.

2-Isopropyl-6-methyl-4-hydroxypyrimidine (IMHP), the specific metabolite of diazinon, urinary levels were measured in a subsample of the National Health and Nutrition Examination Survey (NHANES III) of 2001–2002 participants aged 6–59 years. Most of the measurements of IMHP in urine were below the limit of detection. IMHP was detected in the 95th percentile at mean concentrations of 1.45 µg/L for the 6–11–year-old age group and 1.35 µg/L for the non-Hispanic blacks ethnicity group (CDC 2005). In a previous nonrandom sample of adults and children in the United States, IMHP levels in urine ranged from non-detectable to 10 µg/L (CDC 2005).

Priority Recommendation: The identified data need to collect additional information is not considered priority. Reference range concentrations of IMHP, a metabolite specific to diazinon, in urine are available for the adult populations (CDC 2005). ATSDR acknowledges that reference concentration data can support exposure and health assessments at waste sites, but the Agency also continues to recognize the importance of collecting additional data on uniquely exposed populations at waste sites. Therefore, the identified data need is not considered priority at this time.

d. Exposures of Children

Purpose: To determine if adequate data on exposures of children to diazinon are available for the purpose of conducting meaningful follow-up exposure and health studies.

***Finding*:** A data need to conduct additional studies to assess exposures of children to diazinon has been identified.

Children are likely to be exposed to diazinon via the same routes that affect adults, such as inhalation of contaminated air, ingestion of contaminated groundwater used as a source of drinking water, ingestion of contaminated food, and dermal contact with contaminated soils and surfaces. In addition, small children are more likely than adults to come into intimate contact with yard dirt, lawns, and house (carpet) dust. Diazinon residues bound to soil or dust particles in carpets or on bare floors may present an exposure route for infants and toddlers through dermal contact and oral ingestion. The potential for young children to ingest soil through hand-to-mouth activity is well documented. In a study of pesticide exposure to children in the home in rural areas in California, samples of house dust had diazinon concentrations (excluding non-detects) ranging from 0.7 to 169 mg/kg in four farmworker homes and from 0.2 to 2.5 mg/kg in three non-farmworker homes (Bradman et al. 1997). For children in two of the homes with the highest levels of diazinon, ingestion exposures leading to risks for cholinesterase inhibition exceeded the EPA's Office of Pesticide Program's chronic oral reference dose (RfD) of $9x10^{-5}$ mg/kg/day. The home with the highest level (169 mg/kg) also exceeded the EPA subchronic RfD of $9x10^{-4}$ mg/kg/day. Diazinon residues of 220, 125, and 52 ng were detected on the hands of 3 of 11 toddlers. For the child with the highest diazinon level on the hands, exposures leading to risks of cholinesterase inhibition due to diazinon ingestion from hand residues also exceeded the EPA chronic RfD (Bradman et al. 1997). From FDA Total Diet Studies (July 1986–April 1991), it was reported that the mean daily intake of diazinon residues in foods thought to be in the diets of infants and children were 0.0061µg/kg/day for the 6–11-month-old group, 0.0106 µg/kg/day for the 2-year-old group, 0.0037 µg/kg/day for the 14–16-year-old female group, and 0.0052 µg/kg/day for the 14–16-year-old male group (Gunderson 1995). No data were located regarding diazinon in breast milk; therefore, an adequate determination of the importance of this route of child exposure has not been made.

Data are available for body burden measurements in children based on IMHP, a metabolite specific to diazinon, concentrations in urine. IMHP was detected in the 95th percentile at a mean concentration of 1.45 µg/L for the 6–11-year-old age group measured in the NHANES III of 2001–2002 (CDC 2005). Measurements of IMHP in urine were below the limit of detection in the 12–19-year-old age group. In a previous nonrandom sample of adults and children in the United States, IMHP levels in urine ranged from non-detectable to 10 µg/L (CDC 2005). There are no studies available correlating the exposure of children to diazinon and body burden measurements of its metabolites.

Potential childhood exposure to diazinon can be minimized by having children avoid playing near areas of high agricultural use. Diazinon can be transported moderate distances in the air from drift during application. Since diazinon has been detected in house and carpet dust, especially in the homes of workers exposed to diazinon, keeping the house clean and free of dust will also reduce a child's potential exposure.

***Priority Recommendation*:** The identified data need to collect additional information is not considered priority. Reference range concentrations of IMHP, a metabolite specific to diazinon, in urine are available for children (CDC 2005). ATSDR acknowledges that reference concentration data can support exposure and health assessments at waste sites, but the Agency also continues to recognize the importance of collecting additional data on uniquely exposed populations at waste sites. Therefore, the identified data need is not considered priority at this time.

e. Environmental Fate

***Purpose*:** To determine whether the available data are adequate to estimate exposure to diazinon under various conditions of environmental release for purposes of planning and conducting meaningful follow-up exposure and health studies.

***Finding*:** A data need to conduct additional environmental fate studies has been identified.

Diazinon partitions to air, water, soil, and sediment and its properties in these media are well characterized.

In the atmosphere, diazinon is degraded by photochemically-produced hydroxyl radicals and by direct photolysis. Particulate phase diazinon is removed from the atmosphere by wet and dry deposition. The half-life for the vapor phase degradation of diazinon by hydroxyl radicals is estimated as 4 hours (Meylan and Howard 1993). The main oxidation product of diazinon in the atmosphere is diazoxon (Seiber et al. 1993). While the activation process (diazinon to diazoxon conversion) in the air would tend to transform diazinon fairly rapidly, the possibility of atmospheric transport means that diazinon can move some distance from agricultural to non-agricultural areas (Glotfelty et al. 1990a, 1990b; Schomburg et al. 1991; Seiber et al. 1993; Zabik and Seiber 1993).

Diazinon released to water may be subject to both abiotic degradation (i.e., hydrolysis and photolysis) and biotic degradation by microorganisms. It may also be emitted to the atmosphere by volatilization or sorbed to soils and sediments. The rate of abiotic degradation is influenced strongly by pH and temperature, with degradation being more rapid at higher temperatures and lower pH (Chapman and Cole 1982; Garcia-Repetto et al. 1994). Half-life values of diazinon in water samples of varying pH and temperature have been reported as ranging from 1.31 to 99 days (Chapman and Cole 1982; EPA 1976; Frank et al. 1991; Garcia-Repetto et al. 1994). Half-lives reported for degradation of diazinon in water due to photolysis ranged from 42 to 88 days, and it has been suggested that hydrolysis is the primary mode of degradation in water (EPA 1976; Frank et al. 1991). Half-life values measured in natural water and tap water samples were 71 and 79 hours, respectively, indicating rapid degradation where hydrolysis, photolysis, and biodegradation may all be operative processes in the natural water system (Ferrando et al. 1992). Degradation of diazinon in natural waters is largely attributed to microbial activity (Bondarenko et al. 2004; Sharom et al. 1980b). The major degradation product of diazinon in water is IMHP (EPA 2004). While volatilization of diazinon from water surfaces may not be expected to be significant, it can be an important transport process. It was reported that 17% of diazinon added to a model pond volatilized in 24 hours (Sanders and Seiber 1983). Based on its organic carbon partition coefficient (Koc), diazinon in water may be moderately adsorbed by soils and sediments (Sharom et al. 1980a).

In soils, diazinon is moderately mobile under certain conditions, particularly soils with an organic matter content <3%, and can leach from soil into groundwater (Arienzo et al. 1994). Leaching potential can be influenced by soil type, the amount of rainfall, the depth of groundwater, and the extent of degradation. In laboratory tests of sand and organic soil, a total of 95% of diazinon

added to the sand leached after 10 rinses, whereas only 50% leached from the organic soil (Sharom et al. 1980a). The presence of organic solvents will increase the mobility (leachability) of diazinon in soil and increase the potential for groundwater contamination. This situation may arise at hazardous waste disposal sites where pesticide waste residues and cosolvents may be encountered together. Diazinon in soils and sediments can be degraded by hydrolysis, photolysis, and biodegradation. Microbial degradation appears to be the major pathway for degradation in soils; however, under anaerobic conditions, abiotic hydrolysis appears to be the most probable mechanism of degradation (Larkin and Tjeerdema 2000). Factors affecting the rate of diazinon degradation in soil are pH, soil type, organic amendments, soil moisture, and diazinon concentration, with the most favorable conditions for degradation being low pH, high organic content, low diazinon concentration, and higher moisture (Schoen and Winterlin 1987). Diazinon degradation was found to be slightly more rapid under more acidic organic soil conditions (Chapman and Cole 1982). Half-lives of diazinon in different soil types under varying conditions have been reported as ranging from 14 to 153 days (Schoen and Winterlin 1987). The major degradation product of diazinon in soils is IMHP (EPA 2004). It was reported that diazinon hydrolyses to IMHP and that the degradation product is significantly more mobile in soils than its parent compound (Somasundaram et al. 1991). Diazinon can undergo photolysis to IMHP on soil surfaces (Burkhard and Guth 1979).

Whereas partitioning of diazinon in environmental media and properties in these media are well characterized, additional information regarding the persistence and mobility of the major degradation products of diazinon would be useful.

***Priority Recommendation*:** The identified data need is not considered priority. Whereas a need exists regarding the environmental fate of diazinon degradation products, the environmental fate of diazinon itself has been adequately assessed.

f. Bioavailability and Bioaccumulation Potential

***Purpose*:** To determine whether adequate data are available to predict the potential of diazinon to be taken up by people exposed via contaminated air, soil, water, and the food chain, in order to plan and conduct meaningful follow-up exposure and health studies.

***Finding*:** A data need has been identified. The bioavailability of diazinon from contaminated soils needs to be determined.

Diazinon can be absorbed following inhalation, dermal, and oral exposures. Diazinon is rapidly absorbed in the body once ingested (CDC 2005). The most likely route of exposure for persons residing near hazardous waste sites is likely to be oral ingestion of contaminated foods. Absorption through the skin and inhalation is of major concern for exposures of farmers, farm workers, or commercial applicators related to the use of diazinon as an insecticide or nematocide (Davis et al. 1983; Lenhart and Kawamoto 1994; Williams et al. 1987). Additional information on the bioavailability from contaminated soils would also be helpful in assessing the relative importance of ingestion of and dermal contact with contaminated soils as a potential route of human exposure.

Diazinon was found not to significantly bioaccumulate in aquatic organisms. Measured BCF values ranged from 4 to 300, but there were only a few cases where the BCF value for diazinon exceeded 100 (El Arab et al. 1990; Goodman et al. 1979; Keizer et al. 1991; Seguchi and Asaka 1981; Tsuda et al. 1989, 1995, 1997). In experiments where testing was continued for several days after exposure to the diazinon ended, tissue residues generally decreased rapidly within 1–5 days (El Arab et al. 1990; Tsuda et al. 1989, 1995). No studies of bioconcentration or biomagnification of diazinon in plants or terrestrial animals could be located. Biomagnification of diazinon does not appear to occur since this compound is rapidly metabolized and BCFs in aquatic organisms are low.

Priority Recommendation: The identified data need to determine the bioavailability of diazinon from contaminated soils is not considered priority because this is not likely to be the primary exposure route for persons residing near hazardous waste sites.

2. Level III Data Needs

a. Registries of Exposed Persons

***Purpose*:** To help assess long-term health consequences of exposure to diazinon in the environment. The ATSDR Division of Health Studies will be asked to consider this substance for

selection as a primary contaminant to establish a diazinon subregistry of the National Exposure Registry.

***Finding*:** A data need has been identified. Diazinon has been found in at least 25 NPL hazardous waste sites. At this time, no formal registries exist that identify people known to have been exposed to diazinon. The development of an exposure registry should provide an important reference tool to help assess long-term health consequences of exposure to diazinon. It should also facilitate the conduct of epidemiologic or health studies to assess any increased incidence of chronic disease or late-developing effects such as cancer. An effort is currently under way at ATSDR to identify those sites where humans have been exposed to site contaminants. From those identified sites, ATSDR can determine which sites list diazinon as a contaminant and the size of the potentially exposed population.

***Priority Recommendation*:** The identified data need is not considered priority. The development of a diazinon subregistry at this time would not contribute significantly to the current database. The development of an exposure subregistry should await the results of needed studies including information on exposure levels in populations living near hazardous waste sites.

B. Toxicity Data Needs (Table 2)

The five remaining "prioritizing" tenets presented in the Decision Guide address toxicity data needs.

- Studies available for all toxicological profile substances to characterize target organs and dose response.
- Disposition studies and comparative physiologically-based pharmacokinetics when a toxic end point has been determined and differences in species response have been noted.
- Mechanistic studies on substances with significant toxicity and substantial human exposure.
- Investigation of methods for mitigation of toxicity for substances where enough is known about mode of action to guide research.
- Epidemiologic studies that will provide a direct answer on human disease for a substance of known significant toxicity.

The following is a brief summary of the toxicity data needs for diazinon. Please refer to the ATSDR Toxicological Profile for Diazinon, chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 2008). Generally, ATSDR believes that the most relevant route(s) of human exposure to diazinon at waste sites is oral, thus ATSDR scientists believe that the proposed toxicity studies should be conducted via the oral route. Additionally, animal testing should be conducted on the species with metabolism most similar to humans or the most sensitive species.

1. Levels I & II Data Needs

ATSDR determines Minimal Risk Levels (MRLs) which are defined as estimates of daily human exposure to a chemical that are likely to be without appreciable risk of deleterious effects over a specified duration. In order to derive MRLs for acute, intermediate, and chronic exposure durations, ATSDR evaluates the substance-specific database to identify studies of the appropriate route and duration of exposure. Thus, in order to derive acute MRLs, ATSDR evaluates studies of 14 days or less duration that identify the target organs and levels of exposure associated with these effects. Similar studies are identified for intermediate and chronic duration exposures.

Currently, ATSDR is using tools such as physiologically-based pharmacokinetic modeling and pharmacodynamic modeling to extrapolate data across routes or durations of exposure. ATSDR acknowledges that such extrapolations may be done on a substance-by-substance basis after adequate toxicokinetics information has been collected.

As reflected in the Decision Guide, ATSDR assigns priorities to identified data needs for acute/intermediate (Level I) studies by the most relevant route of exposure at Superfund sites. Regarding the need to conduct studies by other routes of exposure, ATSDR usually first requires toxicokinetic studies for the three routes of exposure to determine the need for the additional route-specific information.

Regarding chronic studies, ATSDR acknowledges that appropriately conducted 90-day studies can generally predict the target organs for chronic exposure. However, they might fall short in accurately predicting the levels of exposure associated with these effects. Although ATSDR acknowledges this fact, it will generally await the results of prechronic and toxicokinetic studies

before assigning priority to chronic toxicity studies. Note: Chronic toxicity studies may be separated from cancer bioassays; they require a one-year exposure.

a. Acute-Duration Exposure

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause acute human health effects.

***Finding*:** A data need to conduct additional studies via inhalation and dermal exposure has been identified. In humans, high-level acute-duration oral exposure to diazinon causes severe AChE inhibition that often leads to cholinergic signs and symptoms, manifested 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) (Adlakha et al. 1988; Bichile et al. 1983; Coye et al. 1987; Dagli et al. 1981; Dahlgren et al. 2004; Hata et al. 1986; Kabrawala et al. 1965; Kamha et al. 2005; Klemmer et al. 1978; Rayner et al. 1972; Reichert et al. 1977; Richter et al. 1992; Schenker et al. 1992; Shankar 1967, 1978; Soliman et al. 1982; Wadia et al. 1974; Wedin et al. 1984). Whereas the acute signs and symptoms of diazinon toxicity in orally-exposed humans are well-characterized, the exposure levels at which these effects begin to occur are usually not known.

Although available oral data clearly implicate the nervous system as the critical target of acute diazinon toxicity, quantitative exposure-response data for the inhalation exposure route are lacking. Available information is restricted to a single report of nasal discharge, polyuria, decreased activity, and salivation in a group of five rats exposed to a diazinon aerosol at a concentration of 2,330 mg/m^3 for 4 hours (Holbert 1989). Additional animal studies are needed to characterize exposure-response data following acute-duration inhalation exposure in order to derive an acute-duration inhalation MRL for diazinon.

Available human data indicate that the nervous system is a sensitive target of diazinon toxicity following acute-duration oral exposure. Animal studies provide adequate insight into the AChE

inhibiting action of diazinon following acute oral exposure. Relatively low level exposure resulted in significant AChE inhibition in the absence of overt clinical signs of neurotoxicity (Davies and Holub 1980a, 1980b; EPA 2000; Moser et al. 2005; Timchalk et al. 2005). Higher exposure levels resulted in cholinergic manifestations including anorexia, ataxia, epistaxis, tremors, listlessness, gasping, convulsions, tachypnea, dyspnea, prostration, fasciculations, twitches, exophthalmos, diarrhea, salivation, diuresis, lacrimation, prostration, Straub tail reflex, and hypothermia (Boyd and Carsky 1969; Chow and Richter 1994; Earl et al. 1971; EPA 1996, 2000; Harris and Holson 1981; Moser 1995; Moser et al. 2005; Robens 1969). An acute-duration oral MRL of 0.006 mg/kg/day was derived for diazinon based on a no-observed-adverse-effect level (NOAEL) of 0.6 mg/kg/day and a lowest-observed-adverse-effect level (LOAEL) of 1.2 mg/kg/day for greater than 20% RBC AChE inhibition in rats examined following 12 days of dietary exposure to diazinon (Davies and Holub 1980a). Additional acute-duration oral exposure studies are not necessary.

Information regarding adverse health effects associated with acute-duration dermal exposure to diazinon is limited. Lee (1989) reported symptoms of respiratory, cardiovascular, gastrointestinal, hematological, and neurological effects in two female gardeners after a diazinon-containing solution was accidentally spilled on the skin. Matsushita et al. (1985) reported diazinon-induced contact dermatitis in farm workers. In another report, a 1% diazinon solution in a skin patch did not elicit irritation or cause sensitization in humans (Lisi et al. 1987). Health effects such as nasal discharge, defecation and diarrhea, erythema and edema, and tremors were noted in studies designed to assess lethality in laboratory animals following acute-duration dermal exposure to diazinon (EPA 1990; Gaines 1960). Skin erythema was noted in guinea pigs following 24-hour occluded dermal exposure to 10 or 20% diazinon solutions, but not 0.5–5% solutions; challenge with 0.05 or 0.5% diazinon solutions resulted in delayed contact hypersensitivity (Matsushita et al. 1985). A single dermal application in rats at a dose level of 65 mg/kg resulted in 52% RBC AChE inhibition. A well-designed multiple-dose acute dermal toxicity study in an animal species is needed to characterize exposure-response relationships for acute-duration dermal exposure.

***Priority Recommendation*:** The identified data need to conduct additional studies via inhalation and dermal exposure is not considered priority because inhalation and dermal exposures are not considered primary routes of exposure to diazinon for populations living near hazardous waste sites.

b. Intermediate-Duration Exposure

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause subchronic human health effects.

Finding: A data need to conduct additional intermediate-duration studies via inhalation and dermal exposure has been identified. No data are available for effects of intermediate-duration inhalation exposure to diazinon in humans. Results of one intermediate-duration inhalation study (Hartman 1990) in rats identify AChE inhibition as a critical effect in diazinon poisoning. An intermediate-duration inhalation MRL of 0.01 mg/m^3 was derived for diazinon based on a NOAEL of 1.57 mg diazinon/m^3 and a LOAEL of 11.6 mg diazinon/m^3 for >20% RBC AChE inhibition in rats exposed to aerosolized diazinon for 6 hours/day, 5 days/week for 21 days (Hartman 1990).

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

Several oral studies identify AChE inhibition as the most sensitive effect of diazinon toxicity in laboratory animals orally exposed to diazinon for periods ranging from 28 to 92 days (Barnes 1988; Davies and Holub 1980a, 1980b; EPA 1996, 2000; Singh 1988). Collectively, these studies indicate that the threshold for toxicologically significant AChE inhibition occurs in rats and dogs at repeated oral dose levels between 0.2 and 2 mg diazinon/kg/day. An intermediate-duration oral MRL of 0.002 mg/kg/day was derived for diazinon based on benchmark dose analysis of diazinon-induced RBC AChE inhibition in rats fed diazinon daily for 42 days (Davies and Holub 1980a). A benchmark response of 20% RBC AChE inhibition was selected as the point of departure for deriving the MRL; the resulting $BMDL_{20}$ was 0.2238 mg/kg/day. Results of other animal studies support this MRL. There is some indication of sensitive developmental toxicity end points (neurological, reproductive, immunological) in pups of mice orally exposed to

diazinon throughout gestation at nonmaternally toxic doses (Barnett et al. 1980; Spyker and Avery 1977). As discussed in the Developmental Toxicity section, a well-designed developmental toxicity study using oral exposure levels up to and including those eliciting maternal toxicity is needed to more extensively assess the potential for diazinon to adversely affect developing neurological, reproductive, and immunological systems.

No data are available regarding health effects in humans following intermediate-duration dermal exposure to diazinon. Limited animal data are available for intermediate-duration dermal exposure to diazinon. Bleakley et al. (1979) reported significant elevations in total fecal porphyrin excretion (indicative of disturbed hepatic porphyrin metabolism) in rats following daily cutaneous exposure to 114 or 229 mg diazinon/kg for up to 12 weeks. Skin sensitization was not observed in guinea pigs treated periodically to 6-hour occluded dermal patches containing diazinon and challenged on study day 36 (Kuhn 1989). The reports of Bleakley et al. (1979) and Kuhn (1989) did not include assessment of cholinesterase activity, which is considered to be the most sensitive systemic effect of diazinon toxicity. Additional animal studies are needed to characterize exposure-response relationships for diazinon-induced neurological effects following intermediate-duration dermal exposure.

***Priority Recommendation*:** The identified data need to conduct additional studies via inhalation and dermal exposure is not considered priority because inhalation and dermal exposures are not considered primary routes of exposure to diazinon for populations living near hazardous waste sites.

c. Chronic-Duration Exposure

(1) Toxicity Assessment

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause chronic human health effects.

***Finding*:** A data need to conduct additional studies via inhalation and dermal exposure has been identified. No human or animal studies are available regarding health effects associated with chronic inhalation exposure to diazinon. A well-designed chronic-duration inhalation study in an

appropriate animal species is needed in order to assess exposure-response relationships following chronic inhalation exposure to diazinon.

No human data are available regarding health effects associated with chronic oral exposure to diazinon. The chronic oral toxicity of diazinon was assessed in two available animal studies, a 98-week feeding study in rats (Kirchner et al. 1991) and a 52-week feeding study in dogs (Rudzki et al. 1991). These studies identified RBC AChE inhibition as the most sensitive effect of diazinon toxicity. A chronic-duration oral MRL of 0.0007 mg/kg/day was derived for diazinon based on a NOAEL of 0.065 mg/kg/day and a LOAEL of 5.5 mg/kg/day for >20% RBC ChE inhibition in rats fed diazinon daily for 98 weeks (Kirchner et al. 1991). The results of the 52-week dog study support the findings in the rats. Clinical signs of diazinon-induced neurotoxicity were not observed in the chronically-exposed rats or dogs at exposure levels up to and including the highest dose groups (Kirchner et al. 1991; Rudzki et al. 1991). Additional chronic-duration oral studies in laboratory animals are not necessary.

No human or animal studies are available regarding health effects associated with chronic dermal exposure to diazinon. A well-designed chronic-duration dermal study in an appropriate animal species is needed in order to assess exposure-response relationships following chronic dermal exposure to diazinon.

***Priority Recommendation*:** The identified data need to conduct additional studies via inhalation and dermal exposure is not considered priority because inhalation and dermal exposures are not considered primary routes of exposure to diazinon for populations living near hazardous waste sites.

(2) Cancer Assessment

***Purpose*:** To determine whether populations potentially exposed to diazinon are at an increased risk for developing cancer for purposes of conducting meaningful follow-up exposure and health studies. Similar to toxicity end point assessment, when bioassays are indicated because of the potential for substantial exposure and the lack of information on carcinogenicity, ATSDR will generally only assign priority to a bioassay conducted via the most relevant route of human exposure at Superfund sites.

Comparative toxicokinetic information across routes as previously discussed will be assigned priority and conducted before assigning priority to any additional routes of exposure. In cases where the assessment of chronic toxicity and carcinogenicity can be combined, they will.

***Finding*:** A data need to conduct additional studies for the carcinogenicity of diazinon via inhalation and dermal exposure has been identified. Available epidemiological studies are inadequate for assessing the carcinogenic potential of diazinon. 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 multiple routes of exposure) studies. No animal studies have assessed the carcinogenicity of diazinon via inhalation exposure. A well-designed inhalation carcinogenicity study using two animal species is needed to adequately assess the potential carcinogenicity of diazinon by the inhalation exposure route.

The carcinogenicity of diazinon was assessed in cancer bioassays conducted in rats and mice administered diazinon in the feed for 103 weeks (NCI 1979). Estimated doses to the rats were 0, 20, and 40 mg diazinon/kg/day. There was no appreciable treatment-related effect on survival or body weights of rats or mice. The study authors noted some hyperactivity in diazinon-treated rats and mice. Tissue masses were noted especially in high-dose male and low-dose female rats. In male rats, lymphomas and leukemias were significantly 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). There were no significantly increased incidences of other tumor types in diazinon-treated male rats or any tumor type in diazinon-treated female rats. Estimated doses to the mice were 0, 13, and 26 mg diazinon/kg/day. An elevation in hepatocellular adenomas and carcinomas was observed in low-dose (20 of 46), but not high-dose (13 of 48) male mice, relative to controls (5 of 21). There were no significantly increased incidences of other tumor types in diazinon-treated male mice or any tumor type in diazinon-treated female mice. The NCI (1979) concluded that diazinon was not carcinogenic to either sex of rats or mice under the study conditions of the bioassays. In light of the fact that the bioassays included dose levels of sufficient magnitude to elicit clinical signs of neurotoxicity in the absence of a carcinogenic effect, it does not appear necessary to conduct additional oral carcinogenicity bioassays for diazinon.

No animal studies have assessed the carcinogenicity of diazinon via dermal exposure. A well-designed dermal carcinogenicity study using two animal species is needed to adequately assess the potential carcinogenicity of diazinon by the dermal exposure route.

The DHHS has not classified diazinon as to its carcinogenicity. Diazinon is not included in the list of chemicals evaluated for carcinogenicity by IARC (2006). EPA (2006) lists diazinon as Cancer Group E (evidence of noncarcinogenicity for humans) according to EPA (1986) cancer guidelines; as of August, 2006, diazinon had not been evaluated under the revised EPA (2005) cancer guidelines.

***Priority Recommendation*:** The identified data need to conduct additional studies via inhalation and dermal exposure is not considered priority because inhalation and dermal exposures are not considered primary routes of exposure to diazinon for populations living near hazardous waste sites. Furthermore, available carcinogenicity animal data for the oral exposure route provide no evidence for the carcinogenicity of diazinon.

d. Genotoxicity

***Purpose*:** To evaluate the mechanism of diazinon-induced toxicity for purposes of future mitigation activities. Generally, priority is assigned genotoxicity studies if information is lacking to assess the genotoxic potential of this substance both *in vivo* (mouse micronucleus) and *in vitro* (Ames *Salmonella*). This is particularly true if there are human data to suggest that the substance may act by a genotoxic mechanism to cause cancer, reproductive toxicity, etc., or there exists "structural alerts" that suggest that the substance may be genotoxic. Additional studies will not be assigned priority simply to confirm or refute an equivocal database without justification.

***Finding*:** A data need to conduct additional genotoxicity studies has been identified. Chronic occupational exposure to multiple insecticides, including diazinon, has been associated with an increased incidence of chromosomal aberrations and increased sister chromatid exchanges in peripheral blood lymphocytes as compared with nonexposed populations (De Ferrari et al. 1991; Kiraly et al. 1979; See et al. 1990). However, these effects could not be specifically attributed to diazinon. Significantly increased sister chromatid exchanges were noted in peripheral blood lymphocytes from a group of volunteers following exposure to a sheep-dip formulation (approximately 45% diazinon) (Hatjian et al. 2000). However, the specific role of diazinon could

not be determined because the formulation contained other ingredients as well. Diazinon (95% purity) induced mutations in a wing somatic mutation and recombination test (SMART) of *Drosophila melanogaster* (Çakir and Sarikaya 2005). Diazinon did not induce sister chromatid exchanges in the bone marrow of mice administered diazinon (88% purity) in single 100 mg/kg gavage dose (EPA 1990). Results of *in vitro* laboratory testing for diazinon-induced genotoxicity in mammalian cells and microorganisms are equivocal. Diazinon induced gene mutations in one Ames assay of *Salmonella typhimurium* in the presence (but not the absence) of metabolic activation (Wong et al. 1989). The chemical was not mutagenic in other Ames assays either with (Kubo et al. 2002) or without (Kubo et al. 2002; Marshall et al. 1976) metabolic activation. Diazinon did not induce gene mutation in the rec-assay utilizing strains of *Bacillus subtilis* tested without metabolic activation (Shirasu et al. 1976). In one mouse lymphoma mutagenicity assay, diazinon elicited a mutagenic response in the absence of metabolic activation (McGregor et al. 1988). However, mutagenicity was not indicated in a similar assay of mouse lymphoma cells either with or without metabolic activation (EPA 1989). Diazinon induced chromosomal aberrations in Chinese hamster cells with metabolic activation (Matsuoka et al. 1979), but tested negative for chromosomal aberrations in human peripheral blood lymphocytes (Lopez et al. 1986). Negative results were obtained in a test for sister chromatid exchanges in Chinese hamster V79 cells, both with and without metabolic activation (Chen et al. 1982) and in a test for micronuclei in cultured rat hepatocytes (Frölichstahl and Piatti 1996). A weakly positive result was obtained for micronuclei in cultured human peripheral blood lymphocytes exposed to diazinon at a concentrations ranging from 0.04 to 4 μg/mL (Bianchi-Santamaria et al. 1997). Diazinon-induced DNA damage was reported in a Comet assay using human primary nasal mucosal cells (Tisch et al. 2002). Diazinon inhibited DNA synthesis in transformed PC12 pheochromocytoma and C6 glioma cells (Qiao et al. 2001), as well as fetal rat astrocytes and human 1321N1 astrocytoma cells (Guizzetti et al. 2005). The available data are inadequate to thoroughly assess the genotoxic potential of diazinon; additional studies, particularly *in vivo* assays, are needed.

***Priority Recommendation*:** The identified data need to conduct additional genotoxicity is not considered priority. Although *in vivo* genotoxicity studies are needed to more completely assess the genotoxic potential of diazinon, these studies are not given priority because diazinon has not been shown to be carcinogenic by the oral exposure route, which is the route of primary concern to populations living near hazardous waste sites.

e. Endocrine Disruption

***Purpose*:** To determine whether populations potentially exposed to diazinon are at an increased risk to develop toxicity of the endocrine system for purposes of conducting meaningful follow-up exposure and health studies. Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior.

Generally, when considering the need to assign priority, in the absence of all information on this end point, ATSDR will assign priority to screening studies that examine effects on a) male and female reproductive organs, and b) other endocrine organs including hypothalamus, pituitary, thyroid, parathyroid, adrenal, pancreas, paraganglia, and pineal body. Such screening level studies include, but are not limited to, *in vitro* studies [e.g., 1) Estrogen Receptor Binding/Transcriptional Activation Assay, 2) Androgen Receptor Binding/Transcriptional Activation Assay, and 3) Steroidogenesis Assay with Minced Testis], and *in vivo* studies [e.g., 1) Rodent 3-day Uterotropic Assay, 2) Rodent 20-day Pubertal Female Assay with Thyroid, 3) Rodent 5–7-day Herschberger Assay].

If any of the following is true, then ATSDR will consider assigning Level II priority to 2-generation reproductive studies: if (1) there are suggestions that diazinon may have endocrine disrupting potential from Level I studies; or (2) if there have been human anecdotal reports of endocrine disrupting effects following diazinon exposure; or (3) if there are structurally similar compounds that affect the endocrine system.

As before, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to studies conducted via additional routes of exposure.

***Finding*:** A data need to conduct additional studies on the endocrine system via inhalation, oral, and dermal exposure has been identified. There are no human data on the potential of diazinon to disrupt the endocrine system. No data are available regarding diazinon-induced hormonal effects (e.g., measurements of serum hormone levels) in animals. No treatment-related morphological or functional effects on reproductive systems were seen in rats, mice, or rabbits administered diazinon orally at doses up to and including those eliciting maternal toxicity (Giknis 1989; Green 1970; Harris and Holson 1981; Infurna and Arthur 1985; Spyker and Avery 1977). There was no histopathological evidence of diazinon-induced effects on reproductive organs of male or female rats or dogs chronically exposed to diazinon in the diet at doses up to and including those eliciting neurotoxic effects (Barnes 1988; Kirchner et al. 1991; Rudzki et al. 1991; Singh 1988). One study reported testicular atrophy and arrested spermatogenesis in three male dogs administered encapsulated diazinon at a dose level of 20 mg/kg/day for 8 months (Earl et al. 1971); however, one of three dogs died and there was significant weight loss, indicating that the testicular effects were likely secondary to emaciation. Delayed maturation of reproductive tissues was reported in mouse pups at oral doses to pregnant dams that did not elicit maternal toxicity (Spyker and Avery 1977). However, no data are available to indicate a possible mechanism of action for this effect. Results of available *in vitro* assessments of diazinon estrogenicity indicate a potentially weak estrogenic effect at best. Diazinon did not induce cell proliferation of estrogen-responsive human breast cells (MCF-7) in the E_SCREEN assay for estrogenicity (Soto et al. 1995). Diazinon was not estrogenic in a yeast two-hybrid assay at concentrations up to and including the highest concentration tested ($1x10^{-4}$ M) (Nishihara et al. 2000). Results of the E-CALUX assay indicated a weakly positive response at a diazinon concentration of $4.6x10^{-4}$ M (Kojima et al. (2005). Collectively, the available *in vivo* data from oral animal studies and *in vitro* assays do not indicate that diazinon has endocrine disrupting activity. No *in vivo* data are available for inhalation or dermal exposure routes, indicating a need for screening data (e.g., reproductive and other endocrine histopathology in inhalation and dermal studies).

***Priority Recommendation*:** The available data on reproductive function and histology of reproductive and endocrine tissues in animals orally exposed to diazinon do not generally indicate that the chemical has endocrine disrupting activity, although the delayed maturation of reproductive tissues in mouse pups exposed to diazinon *in utero* indicates a potential diazinon-induced effect on the endocrine system. The identified data need to conduct additional studies on the endocrine system via oral exposure is not considered priority pending the results of a well-designed developmental toxicity study that includes assessment of endocrinological end points.

The identified data need to conduct additional studies on the endocrine system via inhalation and dermal exposure is not considered priority because inhalation and dermal exposures are not the exposure route of primary concern for populations living near hazardous waste sites.

f. Reproductive Toxicity

***Purpose*:** To determine whether populations potentially exposed to diazinon are at an increased risk to develop reproductive effects for purposes of conducting meaningful follow-up exposure and health studies. ATSDR scientists believe it is important to acquire reproductive toxicity data in order to consider the needs of susceptible populations. It is desirable to have information on reproductive toxicity before developing MRLs to ensure that target organs have been adequately evaluated.

Generally, when considering the need to assign priority, in the absence of all information on this end point, ATSDR will assign priority to the conduct of 90-day studies with special emphasis on reproductive organ pathology. If any of the following is true, then ATSDR will consider assigning priority to multigeneration animal studies: (1) If any indication is found in these studies that the reproductive system of either male or female animals is a target organ of substance exposure; or (2) if there have been human anecdotal reports of reproductive effects following substance exposure; or (3) if there are structurally similar compounds that affect reproduction.

As before, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to studies conducted via additional routes of exposure.

***Finding*:** A data need to conduct additional reproductive studies via inhalation, oral, and dermal exposure has been identified. No information is available regarding the reproductive toxicity of diazinon in humans. Information regarding the reproductive toxicity of diazinon in animals is restricted to studies that employed the oral exposure route. No comprehensive multiple-dose multigeneration reproductive toxicity studies were located. One 4-generation reproduction study in rats employed a single oral exposure level (1 ppm diazinon in the diet) and found no adverse effects on number of pregnant dams, number of pups, or mean litter sizes (Green 1970). Litter size was reduced (approximately 20% lower than controls) in pregnant rats receiving diazinon

orally at a dose of 0.18 mg/kg/day throughout gestation; a higher dose (9 mg/kg/day) was without apparent effect (Spyker and Avery 1977). Testicular atrophy and arrested spermatogenesis were reported in dogs administered diazinon in daily capsule at 10 and 20 mg/kg/day for up to 8 months; however, these effects may have been secondary to emaciation (Earl et al. 1971). No histopathologic evidence of treatment-related effects were seen in reproductive tissues of laboratory animals orally exposed to diazinon for intermediate or chronic durations at dose levels up to and including those eliciting clinical signs of diazinon-induced neurological effects. However, a well-designed multigeneration reproductive toxicity study is needed to adequately assess fertility in animals exposed to diazinon.

***Priority Recommendation*:** The identified data need to conduct additional reproductive toxicity studies via inhalation, oral, and dermal exposure is not considered priority. Results of well-designed oral toxicity studies of subchronic and chronic durations (including a single-generation reproductive toxicity study) do not implicate reproductive tissues as critical toxicity targets of diazinon. Reproductive toxicity studies for inhalation and dermal exposure routes are not considered priority because inhalation and dermal exposure scenarios are not of primary concern for populations living near hazardous waste sites.

g. Developmental Toxicity

***Purpose*:** To determine whether populations potentially exposed to diazinon are at an increased risk for developmental effects for purposes of conducting meaningful follow-up exposure and health studies. Similar to reproductive toxicity assessment, Agency scientists believe it is important to assess the developmental toxicity data.

In the absence of any reproductive or teratologic information, ATSDR will consider proposals to simultaneously acquire reproductive and teratological information. ATSDR acknowledges that, in some circumstances, developmental studies may be assigned priority if the following statements are true: (1) if a two-generation reproductive study provides preliminary information on possible developmental toxicity of diazinon, (2) if there are human anecdotal reports of developmental effects following diazinon exposure, *or* (3) if structurally similar compounds have caused developmental effects.

As for reproductive toxicity, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to the conduct of studies via additional routes of exposure.

***Finding*:** A data need to conduct additional developmental studies via inhalation, oral, and dermal exposure has been identified. No human data are available regarding the potential for diazinon-induced developmental toxicity. Available information in animals is restricted to studies that employed the oral exposure route. Results of one developmental toxicity study indicate that diazinon may cause neurological deficits and delayed maturation of reproductive tissues in pups at oral doses to pregnant mice (0.18 and 9 mg/kg/day on gestation days 1–18) that did not elicit overt maternal toxicity (Spyker and Avery 1977). Results of another study indicate that oral diazinon treatment of pregnant mice at non-maternally toxic dose levels resulted in decreased serum IG_1 levels in pups at 101 days postpartum, but normal levels by day 400 postpartum (Barnett et al. 1980). Other studies found no evidence of developmental toxicity at dose levels eliciting clear clinical signs of maternal toxicity (Harris and Holson 1981; Robens 1969). Well-designed developmental toxicity studies that employ inhalation, oral, and dermal exposure routes could be designed to more extensively assess the potential for diazinon-induced developmental toxicity.

***Priority Recommendation*:** The identified data need to conduct additional developmental toxicity studies via oral exposure is considered priority. A well-designed developmental toxicity study using oral exposure levels up to and including those eliciting maternal toxicity could more extensively assess the potential for diazinon to adversely affect developing neurological, reproductive, and immunological systems. The identified data need to conduct additional developmental toxicity studies via inhalation and dermal exposure is not considered priority because inhalation and dermal exposure scenarios are not of primary concern for populations living near hazardous waste sites.

h. Immunotoxicity

***Purpose*:** To evaluate the mechanism of diazinon-induced toxicity for purposes of defining target organs and future mitigation activities. There is evidence to suggest that the immune system might be a susceptible target organ for many environmental contaminants. In the absence of any information on the immune system as a target organ, priority will be assigned to the evaluation of

the immune system (lymphoid tissue, blood components) as an end point in 90-day studies (Level I) before assigning priority to an immunotoxicology battery as recently defined by the NTP.

For those substances that either (1) show evidence of immune system effects in 90-day studies, (2) have human anecdotal data to suggest that the immune system may be affected, or (3) are structurally similar to known immunotoxicants, an immunotoxicology battery of tests will be assigned priority.

***Finding*:** A data need to conduct additional immunotoxicity studies via inhalation, oral, and dermal exposure has been identified. No human or animal data are available regarding potential for diazinon-induced immunological effects following inhalation exposure. A well-designed animal study by the inhalation exposure route is needed to assess the immunotoxicity of inhaled diazinon.

Available human oral data are restricted to autopsy reports of lymphoreticular damage (spleen, thymus) in persons ingesting high acute doses of diazinon (Limaye 1966; Poklis et al. 1980). High acute oral doses (50–700 mg/kg) of diazinon have been associated with decreased spleen weight, splenic red pulp contraction, reduced thymus weight, and thymic atrophy in rats (Boyd and Carsky 1969). However, 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 receiving up to 212 mg diazinon/kg/day in feed for 13 weeks (Singh 1988) or up to 12 mg diazinon/kg/day for 98 weeks (Kirchner et al. 1991), or in Beagle dogs receiving up to 11.6 mg diazinon/kg/day for 13 weeks (Barnes 1988) or up to 9 mg/kg/day for 52 weeks (Rudzki et al. 1991). Although these results collectively indicate that the adult immunological system may not be a particularly sensitive target of diazinon toxicity at sublethal oral exposure concentrations up to and including those that may induce neurotoxic effects, immune function has not been adequately assessed in orally-exposed animals. Additional animal data are needed to assess the potential for compromised immune function following oral exposure to diazinon.

The potential immunotoxicity of diazinon following dermal exposure has not been studied in detail. A 1% diazinon solution in a skin patch did not elicit irritation or cause sensitization in humans (Lisi et al. 1987). A 24-hour occluded dermal exposure of guinea pigs to 10 or 20% diazinon solutions, followed by challenge with 0.05 or 0.5% diazinon solutions, resulted in delayed contact hypersensitivity (Matsushita et al. 1985). Skin sensitization was not observed in

guinea pigs treated periodically to 6-hour occluded dermal patches containing diazinon and challenged on study day 36 (Kuhn 1989). Additional dermal exposure studies are needed to adequately assess the potential immunotoxicity of diazinon, although the immunological system does not appear to be a particularly sensitive target of diazinon toxicity.

***Priority Recommendation*:** The identified data need to conduct additional immunotoxicity studies via oral exposure is not considered priority pending the results of a well-designed developmental toxicity study that includes assessment of the developing immune system. The identified data need to conduct additional immunotoxicity studies via inhalation and dermal exposure is not considered priority because inhalation and dermal exposure scenarios are not of primary concern for populations living near hazardous waste sites.

i. Neurotoxicity

***Purpose*:** To evaluate the mechanism of diazinon-induced toxicity to define target organs and future mitigation activities. Similar to immunotoxicity, there is a growing body of data to suggest that the nervous system is a very sensitive target organ for many environmental chemicals. In the absence of any information on the nervous system as a target organ, priority will be assigned evaluation of the nervous system as an end point in 90-day studies (Level I) before assigning priority to a neurotoxicology battery.

It may be possible to assign priority to evaluation of demeanor in 90-day studies along with neuropathology. For those substances that either (1) show evidence of nervous system effects in 90-day studies, (2) have human anecdotal data to suggest that the nervous system may be affected, or (3) are structurally similar to known neurotoxicants, a neurotoxicology battery of tests will be assigned priority.

***Finding*:** A data need to conduct additional neurotoxicity studies via inhalation, oral, and dermal exposure has been identified. Diazinon is one of the many widely-studied organophosphate AChE inhibitors. Human and animal data consistently identify the nervous system as the most sensitive target of diazinon toxicity for acute- intermediate-, and chronic-duration exposure. Available neurotoxicity data are derived mainly from accidental or intentional ingestion in humans and oral toxicity studies in animals. One developmental toxicity study included a report of endurance and coordination deficits in offspring of rats administered diazinon during gestation

(Spyker and Avery 1977). A neurotoxicology battery of tests is needed to adequately assess the potential for neurobehavioral deficits in laboratory animals exposed to diazinon.

***Priority Recommendation*:** The identified data need to conduct additional neurotoxicity studies via oral exposure is not considered priority pending the results of a well-designed developmental toxicity study that includes assessment of neurodevelopmental end points. The identified data need to conduct additional neurotoxicity studies via inhalation and dermal exposure is not considered priority because inhalation and dermal exposure scenarios are not of primary concern for populations living near hazardous waste sites.

j. Toxicokinetics

***Purpose*:** To evaluate the disposition of diazinon across species and routes of exposure to elucidate target organs and mechanisms of toxicity, and to assess the need to conduct studies by routes other than the primary route of exposure.

***Finding*:** A data need to assess the toxicokinetics of diazinon following inhalation, oral, and dermal exposure has been identified. No information is available regarding the toxicokinetics of inhaled diazinon in humans or animals, although it is assumed that inhaled diazinon would be readily absorbed. Available studies in volunteers and animals demonstrate the rapid and extensive absorption of diazinon following oral exposure (Abdelsalam and Ford 1986; Garfitt et al. 2002; Iverson et al. 1975; Janes et al. 1973; Machin et al. 1971, 1974; Mount 1984; Mücke et al. 1970; Wu et al. 1996). Absorption of small amounts of dermally-applied diazinon has been demonstrated in volunteers (Garfitt et al. 2002; Wester et al. 1993). Limited information is available regarding distribution of absorbed diazinon. The chemical appears to be widely distributed in humans and animals and is generally understood to be rapidly metabolized and relatively quickly eliminated, predominantly as dialkyl phosphate metabolites in the urine (Abdelsalam and Ford 1986; Garfitt et al. 2002; Janes et al. 1973; Machin et al. 1971, 1974; Mücke et al. 1970; Poklis et al. 1980). The general pharmacokinetic behavior of diazinon is similar in humans and laboratory animals; available comparative data derive mainly from oral exposure. However, potential differences in pharmacokinetic behavior and biotransformation in blood and target tissues, particularly at exposure levels of toxicity concern have not been extensively studied. Therefore, extrapolation from animals to humans includes an appreciable

degree of uncertainty, although available human and animal data identify a common critical target of diazinon toxicity, namely AChE inhibition in central and peripheral nervous tissues.

A physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) model has been developed for predicting the absorption, distribution, metabolism, and elimination of diazinon and two of its metabolites, diazinon-oxon and 2-isopropyl-4-methyl-6-hydroxypyrimidine (IMHP), in rats and humans (Poet et al. 2004). The model also quantifies the inhibition of B-esterases (AChE, butylcholinesterase [BuChE], ChE, and carboxylesterase) activities in blood, RBCs, liver, diaphragm, and brain. The model has been shown to make predictions that are quite similar to observations of blood and tissue levels of diazinon and metabolites from multiple routes of exposure in rats from multiple studies (Poet et al. 2004). The human model also makes predictions of blood, red blood cell, and tissue esterase inhibition, which are important toxicodynamic end points. In humans, the model predicts urine levels of diazinon metabolites from oral and dermal exposures that are very similar to observations; however, the ability of the model to accurately simulate levels of diazinon and diazinon-oxon in human target tissues is unknown. Limitations include the lack of validation of model performance for human blood and tissue levels due to the absence of human data for these end points. An associated limitation is uncertainty in the model to accurately describe esterase inhibition in blood, RBCs, or tissues, including the peripheral and central nervous systems.

Well-designed animal studies are needed to assess the toxicokinetics of inhaled diazinon. Additional comparative studies via the oral exposure route are needed to assist in estimations of target tissue concentrations and resulting esterase inhibition. Additional toxicokinetic studies using the dermal exposure route are needed to quantify the toxicokinetics of diazinon following dermal exposure.

***Priority Recommendation*:** The identified data need to assess the toxicokinetics of diazinon following oral exposure is not considered priority because toxicokinetic data are presently available for this exposure route and provide sufficient information to determine that diazinon is well-absorbed, widely distributed, and rapidly metabolized, followed by excretion mainly via the urine. The identified data need to assess the toxicokinetics of diazinon following inhalation and dermal exposure is not considered priority because inhalation and dermal exposure scenarios are not of primary concern for populations living near hazardous waste sites.

2. Level III Data Needs

a. Epidemiologic Studies

***Purpose*:** To evaluate the extant epidemiologic database and to propose the conduct of additional studies that may lead to cause- and effect- findings. The ATSDR Division of Health Studies will be informed of all candidate substances.

***Finding*:** A data need has been identified. Available information regarding diazinon-associated human health effects derive mainly from case reports of accidental or intentional oral poisoning (Adlakha et al. 1988; Balani et al. 1968; Bichile et al. 1983; Dagli et al. 1981; Dahlgren et al. 2004; DePalma et al. 1970; Kabrawala et al. 1965; Kamha et al. 2005; Klemmer et al. 1978; Lee 1989; Limaye 1966; Poklis et al. 1980; Reichert et al. 1977; Wadia et al. 1974; Wedin et al. 1984; Weizman and Sofer 1992) or epidemiological studies of workers known to be exposed to diazinon (Alavanja et al. 2004; Beane Freeman et al. 2005; Cantor et al. 1992; Davis et al. 1993; Maizlish et al. 1987; Morris et al. 1986; Rayner et al. 1972). Reported adverse effects were typical of those elicited by organophosphate cholinesterase inhibitors. At least some of the reports include exposure of pesticide applicators to diazinon and other pesticides as well. Furthermore, the epidemiological studies do not include quantifiable exposure levels. The database of human data includes a few controlled studies in which volunteers were administered oral doses of diazinon and assessed for plasma ChE levels (EPA 2001). A controlled test for allergic response to single dermal application of diazinon in a group of 294 volunteers was negative (Lisi et al. 1987). There is a data need for information regarding the potential health effects associated with chronic oral exposure to relatively low concentrations of diazinon, particularly in areas surrounding hazardous waste sites that contain diazinon.

Priority Recommendation: The identified data need to conduct epidemiologic studies on diazinon is not considered priority. Diazinon has been detected in a relatively small number of NPL hazardous waste sites in the United States (at least 25 of 1,678 sites) (HazDat 2006). Studies of populations living near sites contaminated with diazinon are likely to be confounded by exposure to other chemicals. If either worker or general populations with appropriate exposures can be identified, epidemiologic studies should be undertaken.

b. Mechanism of Toxic Action

***Purpose*:** To evaluate the mechanism of diazinon-induced toxicity to define target organs and future mitigation activities.

***Finding*:** A data need has not been identified. It is widely understood that diazinon toxicity results predominantly from the inhibition of AChE in the central and peripheral nervous system. As an anticholinesterase organophosphate, diazinon inhibits AChE by reacting with the active site to form a stable phosphorylated complex incapable of destroying acetylcholine at the synaptic gutter between the pre- and postsynaptic nerve endings or neuromuscular junctions of skeletal muscles, which results in accumulation of acetylcholine at these sites and excessive stimulation of cholinergic fibers. Relatively low level exposure to diazinon may result in AChE inhibition in the absence of clinical signs of toxicity. At higher exposure levels, signs and symptoms of toxicity are elicited. Cholinergic actions involving end organs (heart, blood vessels, secretory glands) innervated by fibers in the postganglionic parasympathetic nerves result in muscarinic effects (miosis, excessive glandular secretions, nausea, urinary incontinence, vomiting, abdominal pain, diarrhea, bronchoconstriction or bronchospasm, increased bronchosecretion, vasodilation, bradycardia, and hypotension). Accumulation of acetylcholine at the skeletal muscle junctions and sympathetic preganglionic nerve endings results in nicotinic effects (muscular fasciculations, weakness, mydriasis, tachycardia, and hypertension). Accumulation of acetylcholine at various cortical, subcortical, and spinal levels (primarily in the cerebral cortex, hippocampus, and extrapyramidal motor system) results in central nervous system effects such as respiratory depression, anxiety, insomnia, headache, restlessness, tension, mental confusion, loss of concentration, apathy, drowsiness, ataxia, tremor, convulsion, and coma (Klaassen et al. 1986; Williams and Burson 1985). Although diazinon directly inhibits AChE, its oxidation product, diazoxon (Iverson et al. 1975; Yang et al. 1971) formed in the liver, is an even more potent inhibitor of the enzyme (Davies and Holub 1980a, 1980b; Enan et al. 1982; Harris et al. 1969; Rajendra et al. 1986; Takahashi et al. 1991). The primary cause of death in acute diazinon poisoning is a depression of the neurons in the brainstem (medulla), collectively known as the respiratory center, resulting in loss of respiratory drive or, in the case of managed treatment, cardiac failure due to electrical impulse or beat conduction abnormalities in cardiac muscles (fatal arrhythmias). Other effects, such as bronchoconstriction, excessive bronchial secretions, and paralysis of the respiratory muscles (intercostal muscles and diaphragm) may also contribute to respiratory insufficiency and death. Thus, death results from loss of respiratory drive and

paralysis of the respiratory muscles, or cardiac failure, or both, with attendant asphyxia or cardiac arrest (Klaassen et al. 1986; Shankar 1967, 1978; Williams and Burson 1985).

The mechanism of diazinon toxicity has been well studied; additional studies on mechanisms of toxic action are not needed at this time. If additional critical targets of toxicity are identified, mechanisms of toxic action for such targets should be assessed.

***Priority Recommendation*:** A data need has not been identified. The mechanism of toxic action for diazinon (AChE inhibition) has been well characterized.

c. Biomarkers

***Purpose*:** To evaluate the need to develop additional biomarkers of exposure and effect for purposes of future medical surveillance that can lead to early detection and treatment.

***Finding*:** A data need has been identified. Diazinon undergoes biotransformation to a variety of polar metabolites, which have been detected in the urine and feces of animals. Urinary and fecal excretion of IMHP, diethylthiophosphate (DETP), and diethylphosphate (DEP) have been reported following exposure of animals to diazinon (Iverson et al. 1975; Machin et al. 1975; Mount 1984; Mücke et al. 1970; Seiber et al. 1993; Yang et al. 1971). Analysis of blood samples for the presence of these metabolites represents a potential means of assessing exposure; however, only IMHP is specific for diazinon. Both DEP and DETP have been detected in the urine of exposed insecticide applicators (Maizlish et al. 1987) and volunteers administered diazinon orally or dermally (Garfitt et al. 2002). However, no data were located regarding measured urinary levels of IMHP in humans following known or suspected exposure to diazinon. As diazinon is rapidly metabolized and excreted from the body, metabolite analysis is useful only in the evaluation of recent exposures. Because there are no reports of quantitative associations between metabolite levels and exposure to diazinon in humans, these biomarkers are presently indicative only of exposure and are not useful for dosimetric analysis. No studies were located regarding biomarkers of effect that are specific to diazinon, although such biomarkers are not likely to exist since diazinon shares a common mechanism of toxic action (AChE inhibition) with a multitude of organophosphorus and carbamate pesticides.

***Priority Recommendation*:** The identified data need is not considered priority because there is no disease state that is unique to diazinon exposure. However, further studies designed to quantitate levels of the diazinon-specific metabolite, IMHP, in humans, could provide valuable dosimetric data.

d. Clinical Methods for Mitigating Toxicity

***Purpose*:** To determine whether any efforts are currently under way to mitigate the effects of exposure to diazinon.

***Finding*:** A data need has not been identified. Mitigation of toxicity following exposure to diazinon is common to the group of organophosphate (OP) pesticides that act as AChE inhibitors described in several medical emergency texts (Carlton et al. 1998; Clark 2002; Erdman 2004; Osmundson 1998). No information is available regarding methods to reduce absorption of inhaled OP pesticides such as diazinon. Methods to reduce absorption of ingested OP pesticides include administration of activated charcoal and gastric lavage shortly following ingestion of the poison. In cases of dermal exposure, the contaminated area should be washed with copious amounts of soap and water. Diazinon is rapidly metabolized, with an estimated mammalian biological half-life of 12–15 hours (Iverson et al. 1975; Mücke et al. 1970). Consequently, efforts at reducing body burdens of poisoned persons may not be critical to the outcome and are not indicated in available medical emergency texts. Other mitigating measures are aimed at interfering with the mechanism of action for toxic effects, namely AChE inhibition. Atropine is administered to function as a competitive inhibitor of acetylcholine (ACh) and therefore antagonize the effects of excessive synaptic ACh. Pralidoxime is administered soon after OP poisoning and may help to regenerate active AChE. However, once aging of the OP:AChE complex has occurred, pralidoxime is no longer effective. Diazepam is used for OP-induced seizures and may be used in conjunction with other antidotes to improve survival and prevent development of central nervous system injury or cardiac effects even in the absence of seizures. Other treatments consist of support of respiratory and cardiac function.

***Priority Recommendation*:** A data need has not been identified. The central and peripheral nervous system has been identified as the critical target of diazinon toxicity and the mechanism of toxic action is AChE inhibition, which is common to a multitude of OP and carbamate pesticides.

Present methods for mitigating the toxicity of OP pesticides such as diazinon are adequate at this time.

e. Children's Susceptibility

***Purpose*:** To determine whether adequate data exist to identify potential health effects from exposures to diazinon during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation.

***Finding*:** A data need to conduct additional studies relevant to children's susceptibility via inhalation, oral, and dermal exposure has been identified. One human study reported neurophysiological and neuropsychological deficits and delayed bone growth in young children exposed at home to a formulation of diazinon that was misused to control an infestation of fleas (Dahlgren et al. 2004). Oral exposure of pregnant mice to diazinon at a dose level that did not cause maternal toxicity reportedly resulted in neurological deficits and delayed maturation of reproductive and immunological systems in the offspring (Barnett et al. 1980; Spyker and Avery 1977). Other developmental toxicity studies did not find evidence of developmental toxicity in animals at dose levels up to and including those eliciting maternal toxicity. There is insufficient information regarding potential age-related differences in the toxicokinetics of diazinon. Age-related differences in regulation of selected CYP enzymes, some of which are involved in diazinon metabolism, have been demonstrated (Leeder and Kearns 1997). Garcia-Lopez and Monteoliva (1988) demonstrated that RBC AChE activity in humans increases with age, starting at birth and exceeding 60 years of age. Padilla et al. (2004) demonstrated that diazinon-induced brain AChE inhibition was greater in 17-day-old rats than adult rats and that liver and plasma from young rats possessed much less detoxification capability than adult tissues. These results provide suggestive evidence of age-related differences in the toxicokinetics and AChE-inhibiting effects of diazinon. Additional toxicokinetic studies in animals should be designed to assess potential age-related differences in the toxicokinetics of diazinon. There is no information to suggest possible age-related differences in the mechanism of toxic action for diazinon.

Priority Recommendation: The identified data need to conduct additional studies on children's susceptibility via oral exposure is not considered priority. Priority has been assigned to perform a

well-designed developmental toxicity study in animals exposed by the oral route to more completely assess the potential for diazinon to cause adverse developmental effects such as those reported by Barnett et al. (1980) and Spyker and Avery (1977). Results of the developmental toxicity study should be assessed prior to consideration of assigning priority to age-related toxicokinetic studies for diazinon. Studies by the inhalation and dermal routes are not considered priority because these are not primary routes of exposure for populations living near hazardous waste sites.

IV. Summary: Prioritization of Data Needs for Diazinon

A. Exposure

Application of the hierarchy of research priorities presented in the Decision Guide begins with the evaluation of available analytical methods for diazinon and proceeds through assessing the need for epidemiologic studies. As stated previously, much information is available on diazinon, though some of the studies are very old. This does not mean that data derived from older studies are not adequate. ATSDR agrees with the National Research Council in that it is not appropriate to judge the quality of past and future studies solely by the standards of today.

Building a sound basic data foundation for higher level environmental research via the Decision Guide requires the determination of human exposure levels and media-specific data on diazinon. Although a lot of information is available, a need to evaluate existing data on concentrations of diazinon in contaminated environmental media at hazardous waste sites has been identified.

Furthermore, a need to collect data on levels of diazinon in body tissues and fluids for populations living near hazardous waste sites has been identified. This information is necessary to establish a database that can be used to assess the need to conduct follow-up human health studies of adult and children populations exposed to diazinon.

One effort is now under way at ATSDR that will examine the extant data at the 25 NPL sites at which diazinon has been found. When complete, this database will include maximum concentrations of diazinon in on-site and off-site media, and an indication of relevant routes of exposure. This database will be developed and evaluated before the need to collect additional media-specific data is assigned priority. This database will not, however, supply information on

the levels of diazinon (or its metabolites) in the tissues of adults and children living near hazardous waste sites or other exposed populations such as workers.

Although there is a need to collect data on levels of diazinon in body tissues and fluids for populations living near hazardous waste sites, it is not considered a priority at this time because reference range concentrations of IMHP, a metabolite specific to diazinon urine are available for children and the adult populations (CDC 2005). ATSDR acknowledges that reference concentration data can support exposure and health assessments at waste sites, but the Agency also continues to recognize the importance of collecting additional data on uniquely exposed populations at waste sites.

Thus, on the basis of the findings given in Section II and above, ATSDR is recommending the initiation of research or studies to fill the following exposure priority data needs (Table 3):

- None of the identified exposure data needs are considered to be priority at this time.

B. Toxicity

The toxicity of diazinon has been studied in animals by the inhalation, oral, and dermal exposure routes. The primary target of toxicity is the nervous system where diazinon and diazoxon inhibit the action of AChE, which results in excessive cholinergic stimulation and associated neurotoxicity. Although several developmental toxicity studies in animals found no indication of developmental toxicity at maternal oral doses up to and including those resulting in maternal toxicity, indications of diazinon-induced neurodevelopmental effects and delayed maturation of reproductive and immunologic systems have been reported in other studies. Therefore, an additional developmental toxicity study is needed to confirm or refute the reports of diazinon-induced developmental toxicity in animals.

This nonhuman research need is justified because of the widespread domestic and environmental contamination of diazinon, and the possibility that significant past exposures have affected many people.

Thus, on the basis of the findings given in Section II and above, ATSDR recommends the initiation of research or studies to fill the following toxicity priority data needs (Table 3):

- Developmental toxicity data via oral exposure

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Table 1. Exposure Data Needs

Exposure	Level I	Level II	Level III
Analytical	Methods for parent compound in REM*	Methods for degradation products in REM*	
	Methods for parent compound in blood or urine	Methods for parent compound/metabolites/ biomarkers	
	Structure-activity relationships (SAR)		
Physical chemical properties	Water solubility		
	Volatility/vapor pressure		
	K_{ow}		
	Henry's law		Registries of exposed persons
Exposure levels	Production volume; Use; Release/ disposal (may be used in lieu of monitoring data)	Monitoring in REM*	Human dosimetry studies
		Monitoring for human exposure (personal sampling, biomarkers of exposure, tissue levels)	Epidemiology
			Disease registries
		Exposures of children	
Environmental fate	Aerobic/anaerobic Biodegradation in H_2O Oxidation Hydrolysis Aerosolization Photoreactivity Volatilization Soil adsorption/desorption	Small field plot studies	
		Monitoring for products in REM*	
Bioavailability		Food chain bioaccumulation	
		Availability from REM* (analytical or toxicity) emphasize *in vivo*	

*REM = Relevant Environmental Media

Table 2. Toxicity Data Needs

Toxicity	Level I	Level II	Level III
Single dose exposure	Single dose disposition Skin/eye irritation Acute toxicity		
Repeated dose exposure	14-day by relevant route 90-day subchronic	Comparative toxicokinetics*	
Chronic exposure	Structure-activity relationships (SAR)	1-Year chronic 2-Year bioassay	Epidemiology*
Genotoxicity*	Ames Micronucleus	Additional genotoxicity studies*	Mechanism of toxic action*
Endocrine disruption	*In vivo* & *in vitro* screen	2-Generation reproductive study	
Reproductive toxicity	Extended repro workup in subchronic	2-Generation or continuous breeding	Biomarkers*
			Clinical methods for mitigating toxicity*
Developmental toxicity*	Short term *in vivo* screen*	2-Species developmental*	Children's susceptibility**
Immunotoxicity	Use subchronic results	Immunotox battery	
Neurotoxicity	Neuropath in subchronic	Neurotox battery	
Sensitization	Dermal sensitization		
Carcinogenicity	Use muta & subchronic results	2-Year bioassay	

*Useful data for examining children's susceptibility issues

**Data needed for addressing children's susceptibility issues include genotoxicity (Level II), developmental toxicity (Levels I and II), epidemiology, mechanism of toxic action, biomarkers, and clinical methods for mitigating toxicity (Level III)

Table 3. ATSDR Substance-Specific Applied Research Program for Diazinon

	EXPOSURE		
	Level I	Level II	Level III
Analytical		methods for quantification of degradation products in REM methods for quantification of metabolites in blood samples	
Physical chemical properties		Information on degradation products	
Exposure levels		exp levels in env media exp levels in humans exp levels in children	potential candidate for exposure registry
Environmental fate			
Bioavailability		soil	
	TOXICITY		
	Level I	Level II	Level III
Acute	inhal, dermal		
Repeated	inhal, dermal	toxicokinetics	
Chronic		inhal, dermal	epidem
Genotoxicity		*in vivo*	
Endocrine disruption	inhal, oral, dermal		
Reproductive toxicity		inhal, oral, dermal	biomarkers
Developmental toxicity		inhal, *ORAL*, dermal	
Children’s susceptibility			inhal, oral, dermal
Immunotoxicity	inhal, oral, dermal		
Neurotoxicity	inhal, oral, dermal		
Carcinogenicity		inhal, dermal	

UPPER CASE: Priority Data Needs identified for diazinon

REM = relevant environmental media